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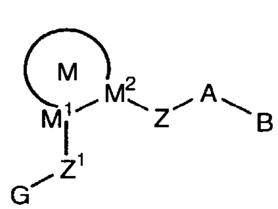
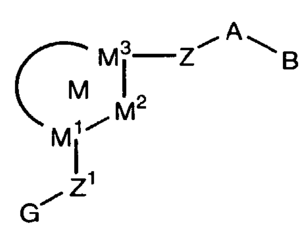
(54) Title: FACTOR XA INHIBITORS



(Ia)



(Ib)

(57) Abstract: This invention relates generally to compounds of formula (Ia) or (Ia) (Ib) that are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

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TITLE

Factor Xa Inhibitors

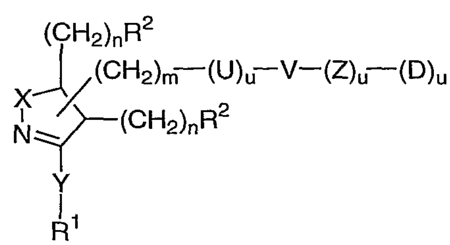
FIELD OF THE INVENTION

This invention relates generally to inhibitors of trypsin-like serine protease enzymes, especially factor Xa, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

BACKGROUND OF THE INVENTION

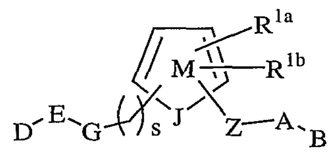
Inhibition of factor Xa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system. Therefore, efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors.

WO97/23212 describes factor Xa inhibitors of the formula:



wherein X can be O. However, WO98/28269 does not disclose compounds like those of the present invention.

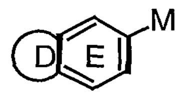
WO98/28269, WO98/28282, and WO99/32454 describe factor Xa inhibitors of the formula:



I

wherein ring M can be a variety of 5-membered heteroaryl rings. These publications do not, however, disclose compounds like those of the present invention.

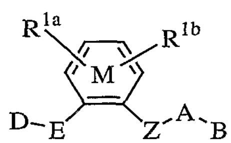
WO98/57951 describes factor Xa inhibitors of the formula:



I

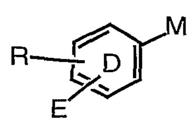
wherein ring D is selected from $-CH_2N{=}CH-$, $-CH_2CH_2N{=}CH-$, a 5-6 membered aromatic system containing from 0-2 heteroatoms selected from the group N, O, and S, ring E contains 0-2 N atom and M is a variety of rings including isoxazoline. WO98/57951 does not, however, disclose compounds like those of the present invention.

WO98/57934 describes factor Xa inhibitors of the formula:



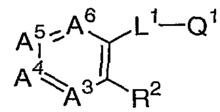
wherein ring M is phenyl or a nitrogen containing heteraromatic. WO98/57934 does not disclose compounds like those of the present invention.

WO98/57937 describes factor Xa inhibitors of the formula:



wherein ring D is phenyl or pyridyl and M is a variety of rings including isoxazoline. However, WO98/57937 does not disclose compounds like those of the present invention.

WO99/00121, WO99/00126, WO99/00127, WO99/00128, describe factor Xa inhibitors of the formula:



wherein L^1 is a linker and Q^1 is a ring system. The publications do not describe compounds that are considered to be part of the present invention.

SUMMARY OF THE INVENTION

One object of the present invention is to provide novel compounds that are useful as factor Xa inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

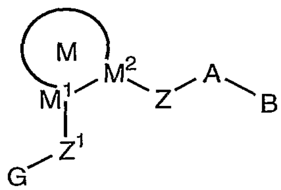
It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide a method for treating thromboembolic disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

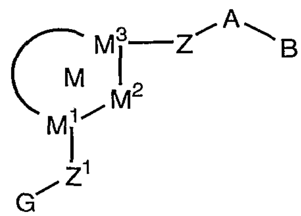
It is another object of the present invention to provide novel compounds for use in therapy.

It is another object of the present invention to provide the use of novel compounds for the manufacture of a medicament for the treatment of a thromboembolic disorder.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of Formula Ia and Ib



Ia

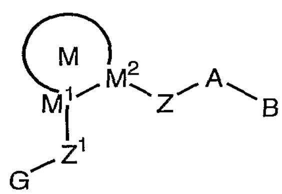


Ib

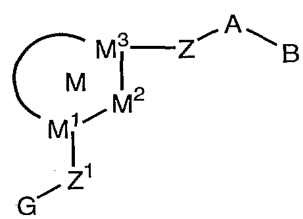
or pharmaceutically acceptable salt or prodrug forms thereof, are effective factor Xa inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in an embodiment, the present invention provides a novel compound of Formula Ia or Ib:



Ia



Ib

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

ring M, including M^1, M^2, and, if present, M^3, is a 5 membered aromatic heterocycle, consisting of: carbon atoms, and 1-4 heteroatoms selected from O, $S(O)_p$, N, and NH;

alternatively, ring M is selected from isoxazoline, isothiazoline, pyrazoline, triazoline, and tetrazoline;

ring M is substituted with 0-2 R^{1a};

G is a group of formula IIa or IIb:

IIa IIb

ring D, including the two atoms of Ring E to which it is attached, is a 5-6 membered non-aromatic ring consisting of carbon atoms, 0-1 double bonds, and 0-2 N, and D is substituted with 0-2 R;

alternatively, ring D, including the two atoms of Ring E to which it is attached, is a 5-6 membered aromatic system consisting of carbon atoms and from 0-2 heteroatoms selected from the group consisting of N, O, and S, and D is substituted with 0-2 R;

E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, and is substituted with 0-2 R;

R is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl$)_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl$)_2$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3;

alternatively, the bridging portion of ring D is absent, ring E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, and ring E is substituted with R^a and R^b;

R^a is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$,

$NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl$)_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl$)_2$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3;

R^b is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl$)_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl$)_2$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3;

alternatively, R^a and R^b combine to form methylenedioxy or ethylenedioxy;

alternatively, the bridging portion of ring D is absent, and ring E is selected from pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, triazolyl, thiophenyl, and thiazolyl, and ring E is substituted with 0-2 R^c;

R^c is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl$)_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl$)_2$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3;

Z is selected from a bond, $-(CR^2R^{2a})_{1-4}-$, $(CR^2R^{2a})_qO(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qNR^3(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qC(O)(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qC(O)O(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qOC(O)(CR^2R^{2a})_{q^1}$,

$(CR^2R^{2a})_qC(O)NR^3(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qNR^3C(O)(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qOC(O)O(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qOC(O)NR^3(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qNR^3C(O)O(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qNR^3C(O)NR^3(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qS(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qS(O)(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qS(O)_2(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qSO_2NR^3(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qNR^3SO_2(CR^2R^{2a})_{q^1}$, and $(CR^2R^{2a})_qNR^3SO_2NR^3(CR^2R^{2a})_{q^1}$, wherein $q + q^1$ total 0, 1, or 2, provided that Z does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

Z^1 is selected from $(CR^3R^{3a})_{1-5}$, $(CR^3R^{3a})_{0-2}CR^3{=}CR^3(CR^3R^{3a})_{0-2}$, $(CR^3R^{3a})_{0-2}C{\equiv}C(CR^3R^{3a})_{0-2}$, $(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)O(CR^3R^{3a})_w$, $(CR^3R^{3a})_uO(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3C(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uOC(O)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3C(O)O(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3C(O)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3C(S)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3S(O)_2(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2NR^3(CR^3R^{3a})_w$, and $(CR^3R^{3a})_uNR^3S(O)_2NR^3(CR^3R^{3a})_w$, wherein u + w total 0, 1, 2, 3, or 4, provided that G_1 does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

R^{1a} is selected from H, $-(CH_2)_r-R^{1b}$, $-CH{=}CH-R^{1b}$, NCH_2R^{1c}, OCH_2R^{1c}, SCH_2R^{1c}, $NH(CH_2)_2(CH_2)_tR^{1b}$, $O(CH_2)_2(CH_2)_tR^{1b}$, $S(CH_2)_2(CH_2)_tR^{1b}$, $S(O)_p(CH_2)_rR^{1d}$, $O(CH_2)_rR^{1d}$, $NR^3(CH_2)_rR^{1d}$, $OC(O)NR^3(CH_2)_rR^{1d}$, $NR^3C(O)NR^3(CH_2)_rR^{1d}$, $NR^3C(O)O(CH_2)_rR^{1d}$, and $NR^3C(O)(CH_2)_rR^{1d}$, provided that R^{1a} forms other than an N-halo, N-N, N-S, N-O, or N-CN bond;

alternatively, when two R^{1a}'s are attached to adjacent atoms, together with the atoms to which they are attached they form a 5-7 membered ring consisting of: carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, this ring being substituted with 0-2 R^{4b} and comprising: 0-3 double bonds;

R^{1b} is selected from H, C_{1-3} alkyl, F, Cl, Br, I, -CN, -CHO, $(CF_2)_rCF_3$, $(CH_2)_rOR^2$, NR^2R^{2a}, $C(O)R^{2c}$, $OC(O)R^2$, $(CF_2)_rCO_2R^{2a}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $C(=NR^{2c})NR^2R^{2a}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NHR^{2b}$, $NR^2C(O)_2R^{2a}$, $OC(O)NR^{2a}R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NR^2(CH_2)_rOR^2$, $SO_2NR^2R^{2a}$, $NR^2SO_2R^{2b}$, C_{3-6} carbocycle substituted with 0-2 R^{4a}, and 5-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-2 R^{4a}, provided that R^{1b} forms other than an N-halo, N-N, N-S, N-O, or N-CN bond;

R^{1c} is selected from H, $CH(CH_2OR^2)_2$, $C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $S(O)R^{2b}$, $S(O)_2R^{2b}$, and $SO_2NR^2R^{2a}$;

R^{1d} is selected from C_{3-6} carbocycle substituted with 0-2 R^{4a}, and 5-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-2 R^{4a}, provided that R^{1d} forms other than an N-N, N-S, or N-O bond;

R^2, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic group substituted with 0-2 R^{4b}, a C_{3-6} carbocyclic-CH_2- residue substituted with 0-2

R^{4b}, and 5-6 membered heterocyclic group comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2a}, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic group substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic group comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic group substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic group comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic group substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic group comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and comprising carbon atoms and from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3b}, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3c}, at each occurrence, is selected from C_{1-4} alkyl, and phenyl;

R^{3d}, at each occurrence, is selected from H, C_{1-4} alkyl, C_{1-4} alkyl-phenyl, and $C(=O)R^{3c}$;

A is selected from:

C_{3-10} carbocyclic group substituted with 0-2 R^4, and

5-12 membered heterocyclic group comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

B is selected from: H, Y, and X-Y, provided that Z and B are attached to different atoms on A;

X is selected from $-(CR^2R^{2a})_{1-4}-$, $-CR^2(CR^2R^{2b})(CH_2)_t-$, $-C(O)-$, $-C(=NR^{1c})-$, $-CR^2(NR^{1c}R^2)-$, $-CR^2(OR^2)-$, $-CR^2(SR^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-SCR^2R^{2a}-$, $-S(O)CR^2R^{2a}-$, $-S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S-$, $-CR^2R^{2a}S(O)-$, $-CR^2R^{2a}S(O)_2-$, $-S(O)_2NR^2-$, $-NR^2S(O)_2-$, $-NR^2S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S(O)_2NR^2-$, $-NR^2S(O)_2NR^2-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)O-$, $-OC(O)NR^2-$,

$-NR^2C(O)NR^2-$, $-NR^2-$, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

Y is selected from:

C_{3-10} carbocyclic group substituted with 0-2 R^{4a}, and

5-12 membered heterocyclic group comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, $(CH_2)_rF$, $(CH_2)_rCl$, $(CH_2)_rBr$, $(CH_2)_rI$, C_{1-4} alkyl, $(CH_2)_rCN$, $(CH_2)_rNO_2$, $(CH_2)_rNR^2R^{2a}$, $C(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $C(=NS(O)_2R^5)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $C(O)NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, $NR^2SO_2-C_{1-4}$ alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, $(CF_2)_rCF_3$, $(CH_2)_r-CF_3$, NCH_2R^{1c}, OCH_2R^{1c}, SCH_2R^{1c}, $N(CH_2)_2(CH_2)_tR^{1b}$, $O(CH_2)_2(CH_2)_tR^{1b}$, $S(CH_2)_2(CH_2)_tR^{1b}$, 5-6 membered carbocycle substituted with 0-1 R^5, and a 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5;

R^{4a}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, $(CF_2)_rCF_3$, $(CH_2)_r-CF_3$, $(CH_2)_r-F$, $(CH_2)_r-Br$, $(CH_2)_r-Cl$, C_{1-4} alkyl, $(CH_2)_rCN$, $(CH_2)_rNO_2$, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $(CH_2)_rN{=}CHOR^3$, $C(O)NH(CH_2)_2NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, $NR^2SO_2-C_{1-4}$ alkyl, $NR^2SO_2R^5$, $C(O)NHSO_2-C_{1-4}$ alkyl, $S(O)_pR^5$, 5-6 membered carbocycle substituted with 0-1 R^5, and a 5-6 membered heterocycle consisting of: carbon atoms and

1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5;

R^{4b}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$, $(CH_2)_r$-F, $(CH_2)_r$-Cl, $(CH_2)_r$-Br, $(CH_2)_r$-I, C_{1-4} alkyl, $(CH_2)_r$-CN, $(CH_2)_r$-NO_2, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $C(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $NR^3SO_2CF_3$, NR^3SO_2-phenyl, $S(O)_pCF_3$, $S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, $(CH_2)_rCF_3$, and $(CF_2)_rCF_3$;

R^5, at each occurrence, is selected from H, C_{1-6} alkyl, =O, $(CH_2)_rOR^3$, F, Cl, Br, I, -CN, NO_2, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $CH(=NOR^{3d})$, $C(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $NR^3SO_2CF_3$, NR^3SO_2-phenyl, $S(O)_pCF_3$, $S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, $(CF_2)_rCF_3$, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

R^6, at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;

R^7, at each occurrence, is selected from H, OH, C_{1-4} alkoxycarbonyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

R^8, at each occurrence, is selected from H, C_{1-6} alkyl, and $(CH_2)_n$-phenyl;

alternatively, R^7 and R^8, when attached to the same nitrogen, combine to form a 5-6 membered heterocyclic ring consisting of carbon atoms and 0-2 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^9, at each occurrence, is selected from H, C_{1-6} alkyl, and $(CH_2)_n$-phenyl;

n, at each occurrence, is selected from 0, 1, 2, and 3;

m, at each occurrence, is selected from 0, 1, and 2;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3;

s, at each occurrence, is selected from 0, 1, and 2;

t, at each occurrence, is selected from 0, 1, 2, and 3; and,

alternatively, Z^1 is absent when:

(a) ring M is pyrrole and G is other than phenyl, pyridyl, pyrimidyl, pyrazinyl, or pyridazinyl, substituted with a group selected from CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, $(CR^8R^9)_tC(O)NR^7R^8$, $(CR^8R^9)_tNR^7R^8$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl$)_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), and $CH_2CH_2N(C_{1-3}$ alkyl$)_2$,;

(b) B is H and at least one R^4 is present and is other than amidino, guanidino, amino-ethylene, or amino-propylene group, any of which may be substituted or cyclized; or

(c) the bridging portion of ring D is absent, and ring E is selected from pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, triazolyl, thiophenyl, and thiazolyl, and ring E is substituted with 0-2 R^c;

provided that when Z^1 is one of $NHCH_2$, $NHCH_2CH_2$, OCH_2, OCH_2CH_2, SCH_2, and SCH_2CH_2, then G is other than phenyl, pyridyl, pyrimidyl, pyrazinyl, pyradazinyl, and piperidinyl, and Y is other than the group $(CH_2)_rNR^2R^{2a}$ or an unsubstituted pyrrolidine, unsubstituted pyrazolidine, unsubstituted imidazolidine, unsubstituted oxazolidine, unsubstituted isoxazolidine, unsubstituted thiazolidine, and unsubstituted isothiazolidine;

provided that when D is absent and B comprises a phenoxy, thiophenyl, sulfinylphenyl, sulfonylphenyl, carboxyphenyl, phenyoxymethyl, or a sulfonamido group, then at least one of R^a and R^b comprises an amino group, an amido group, a nitrilo group, an amidino group, or a guanidino group;

alternatively, when

(a) B is other than an optionally substituted carbocycle; and,

(b) Z^1 is $(CR^3R^{3a})_uNR^3(CR^3R^{3a})_w$ and u+w is 1, 2, 3, or 4, $(CR^3R^{3a})_uC(O)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3C(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2NR^3(CR^3R^{3a})_w$, or $(CR^3R^{3a})_uNR^3S(O)_2(CR^3R^{3a})_w$;

then Z is other than $(CH_2)NR^3$, $NR^3(CH_2)$, $(CH_2)NR^3(CH_2)$, $(CH_2)(CH_2)NR^3$, $NR^3(CH_2)(CH_2)$, $(CH_2)_qC(O)NR^3(CH_2)_{q^1}$, $(CH_2)_qNR^3C(O)(CH_2)_{q^1}$, $(CH_2)_qSO_2NR^3(CH_2)_{q^1}$, or $(CH_2)_qNR^3SO_2(CH_2)_{q^1}$;

alternatively, when

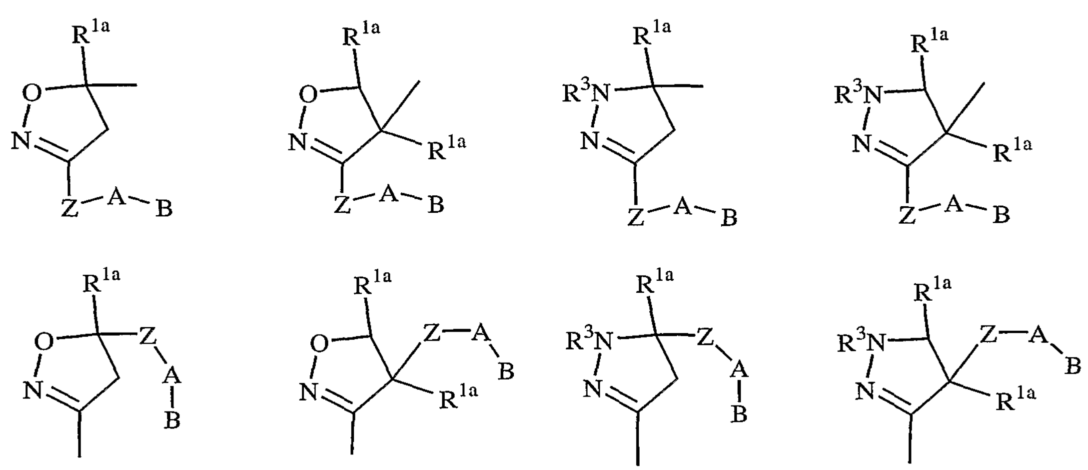
(a) B is other than an optionally substituted carbocycle; and,

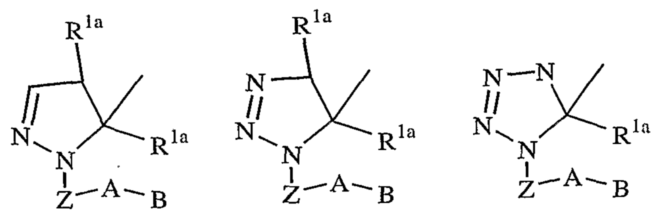
(b) Z is $(CH_2)NR^3$, $NR^3(CH_2)$, $(CH_2)NR^3(CH_2)$, $(CH_2)(CH_2)NR^3$, $NR^3(CH_2)(CH_2)$, $(CH_2)_qC(O)NR^3(CH_2)_{q^1}$, $(CH_2)_qNR^3C(O)(CH_2)_{q^1}$, $(CH_2)_qSO_2NR^3(CH_2)_{q^1}$, or $(CH_2)_qNR^3SO_2(CH_2)_{q^1}$;

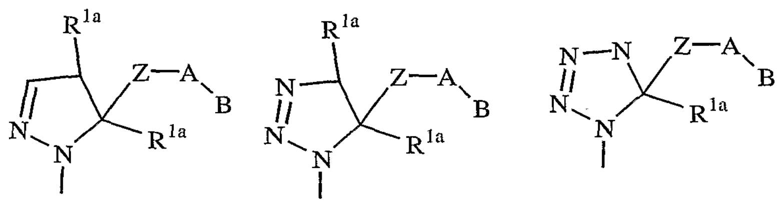
then Z^1 is other than $(CR^3R^{3a})_uNR^3(CR^3R^{3a})_w$ and u+w is 1, 2, 3, or 4, $(CR^3R^{3a})_uC(O)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3C(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2NR^3(CR^3R^{3a})_w$, or $(CR^3R^{3a})_uNR^3S(O)_2(CR^3R^{3a})_w$.

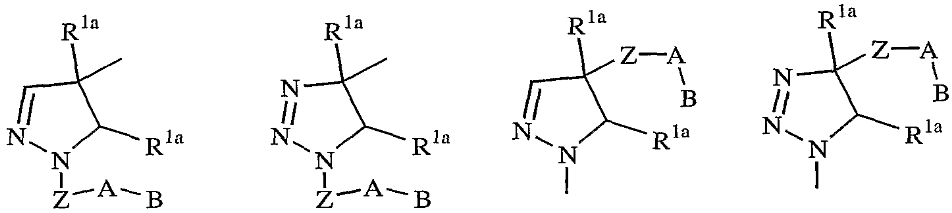
[2] In a preferred embodiment, the present invention provides a compound, wherein:

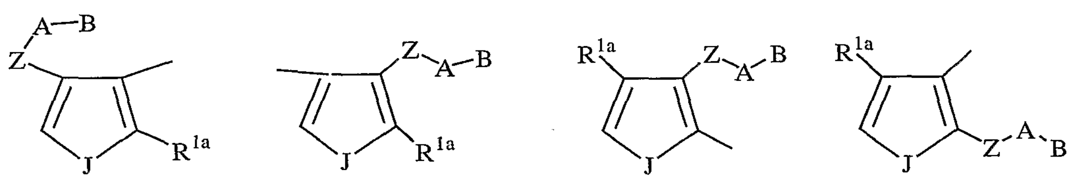
M-Z-A-B is selected from the group:

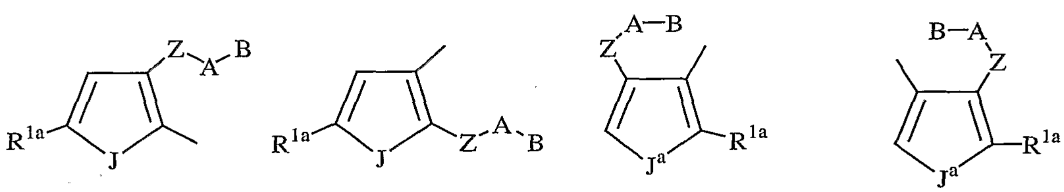


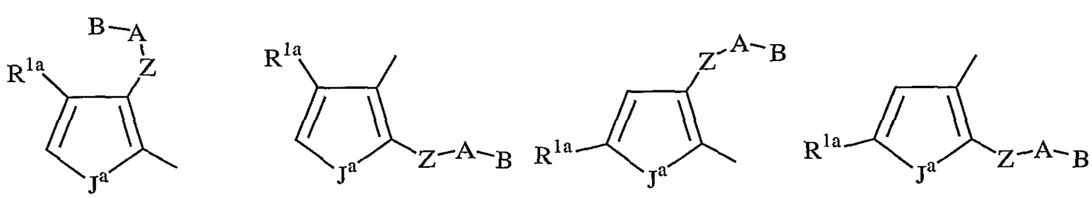


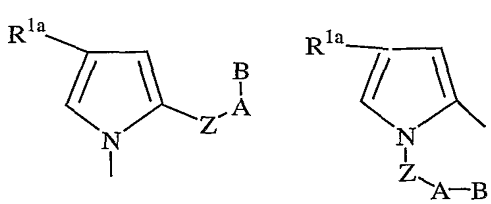


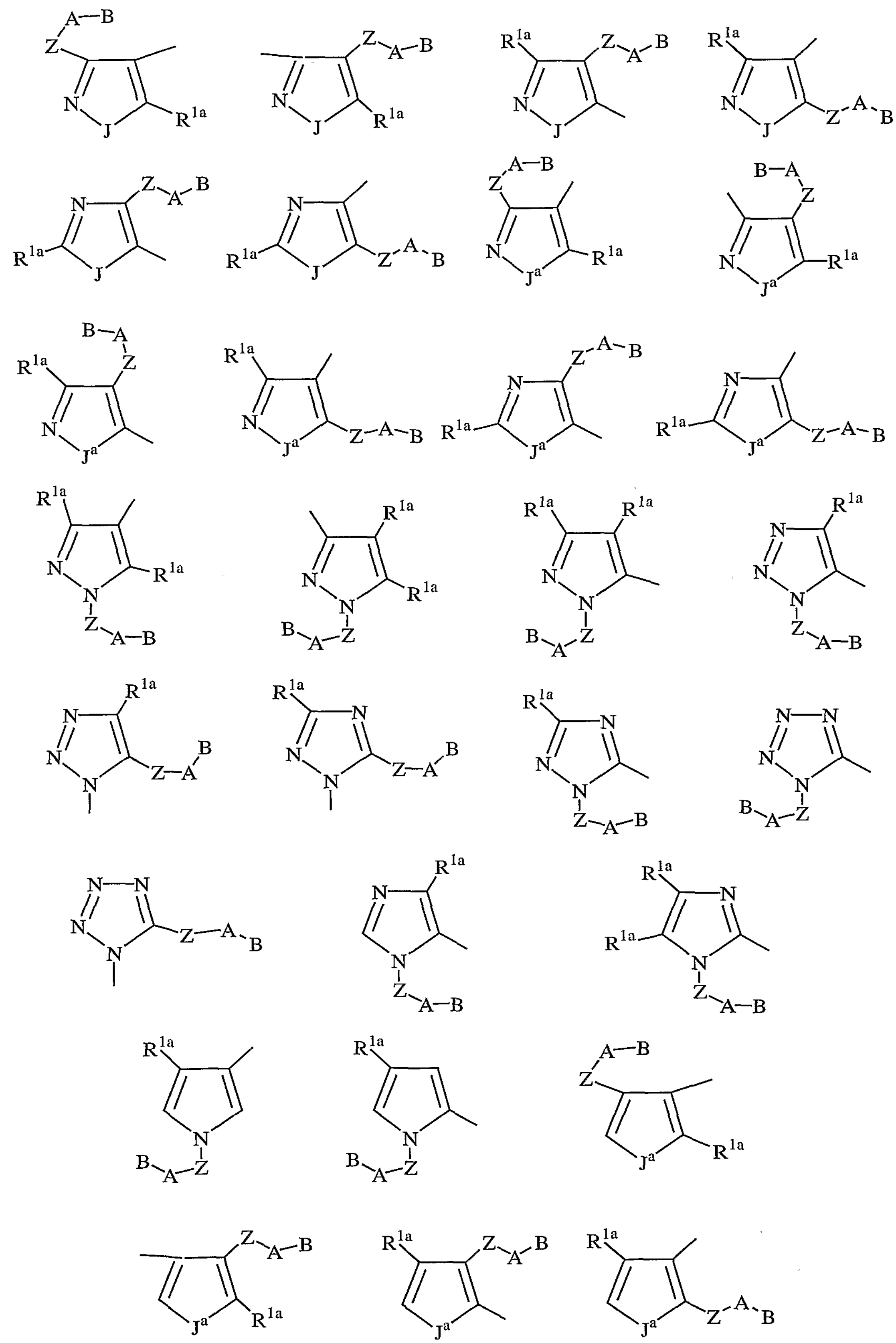


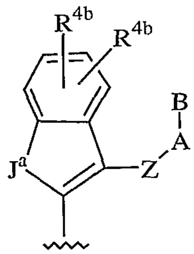












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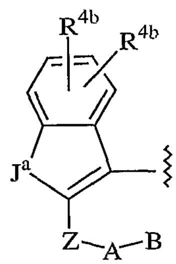

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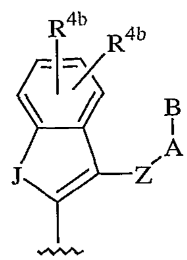

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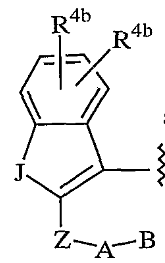

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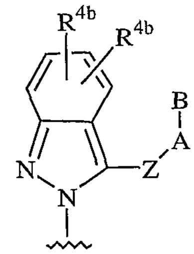


aaa

J is O or S;

J^a is NH or NR^{1a};

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^4;

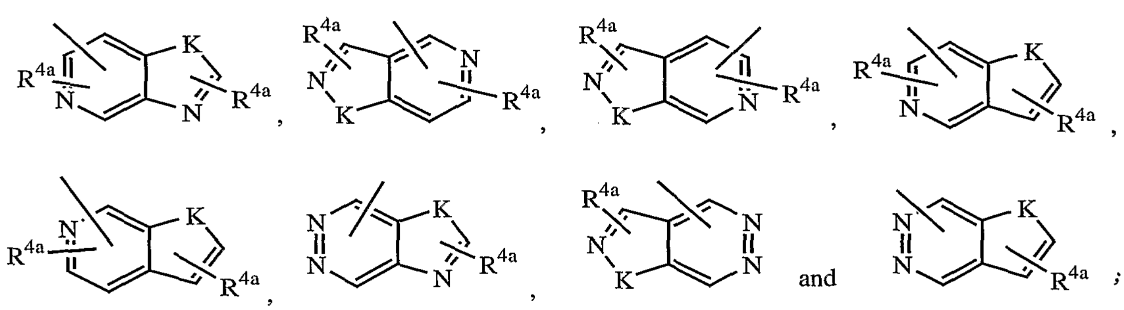
phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

X is selected from $-(CR^2R^{2a})_{1-4}-$, $-C(O)-$, $-C(=NR^{1c})-$, $-CR^2(NR^{1c}R^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)NR^2-$, $-NR^2-$, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

Y is selected from one of the following carbocyclic and heterocyclic systems that are substituted with 0-2 R^{4a};

cyclopropyl, cyclopentyl, cyclohexyl, phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

alternatively, Y is selected from the following bicyclic heteroaryl ring systems:



K is selected from O, S, NH, and N;

Z is selected from a bond, CH_2O, OCH_2, NH, CH_2NH, $NHCH_2$, $CH_2C(O)$, $C(O)CH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that Z does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

Z^1 is selected from $(CR^3R^{3a})_{1-3}$, $(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uO(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3C(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)NR^3(CR^3R^{3a})_w$, and $(CR^3R^{3a})_uS(O)_2NR^3(CR^3R^{3a})_w$, wherein u + w total 0, 1, or 2, provided that G_1 does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $C(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, CF_3, NCH_2R^{1c}, OCH_2R^{1c}, SCH_2R^{1c}, $N(CH_2)_2(CH_2)_tR^{1b}$, $O(CH_2)_2(CH_2)_tR^{1b}$, $S(CH_2)_2(CH_2)_tR^{1b}$, 5-6 membered carbocycle substituted with 0-1 R^5, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5;

R^{4a}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, CF_3, F, Br, Cl, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $C(O)NHSO_2$-C_{1-4} alkyl, $S(O)_pR^5$, 5-6 membered carbocycle substituted with 0-1 R^5, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5;

alternatively, when

(a) B is other than an optionally substituted carbocycle; and,

(b) Z^1 is $(CH_2)_uNR^3(CH_2)_w$ and u+w is 1 or 2, $(CH_2)_uC(O)NR^3(CH_2)_w$, $(CH_2)_uNR^3C(O)(CH_2)_w$, $(CH_2)_uS(O)NR^3(CH_2)_w$, $(CH_2)_uS(O)_2NR^3(CH_2)_w$, or $(CH_2)_uNR^3S(O)_2(CH_2)_w$;

then Z is other than CH_2NH, $NHCH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$;

alternatively, when

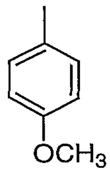
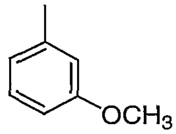
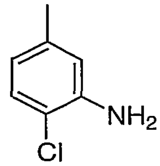
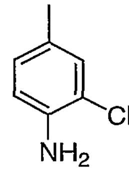
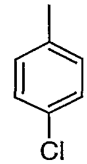
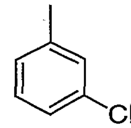
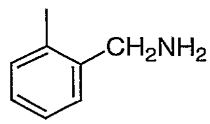
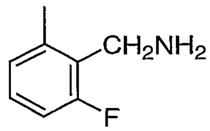
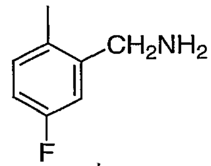
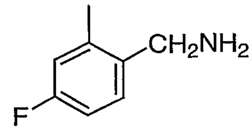
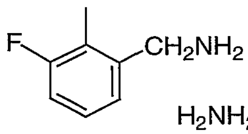
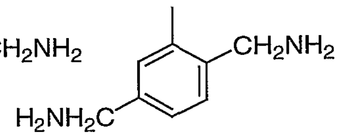
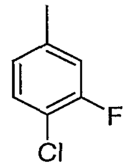
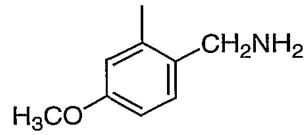
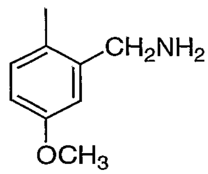
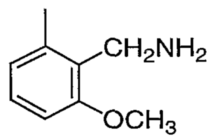
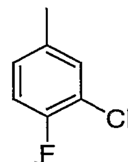
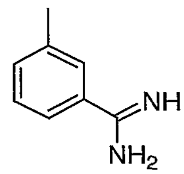
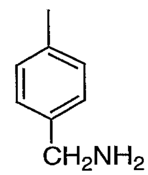
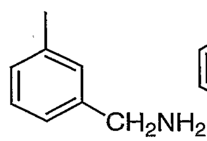
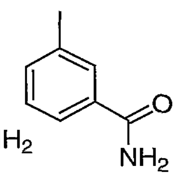
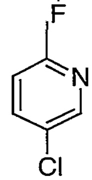
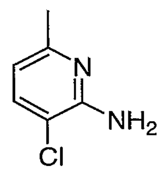
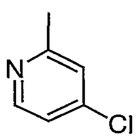
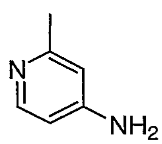
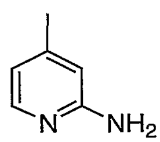
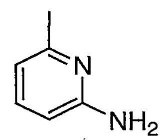
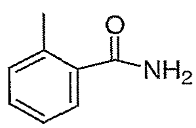
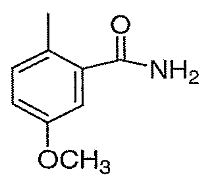
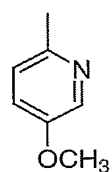
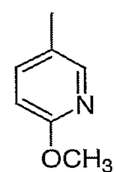
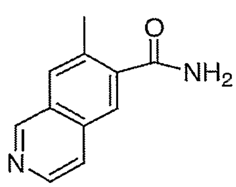
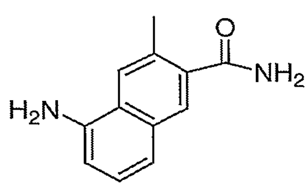
(a) B is other than an optionally substituted carbocycle; and,

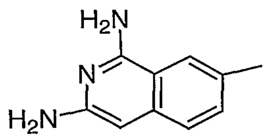
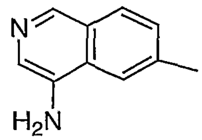
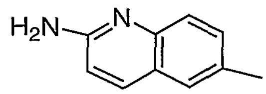
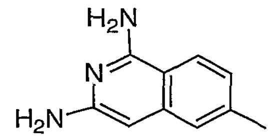
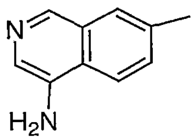
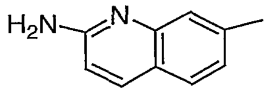
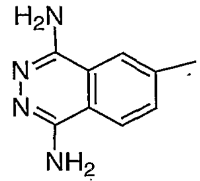
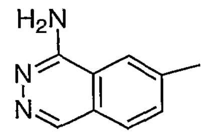
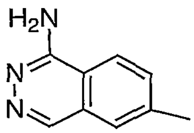
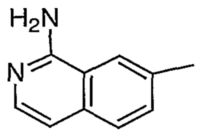
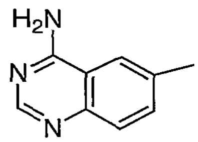
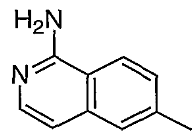
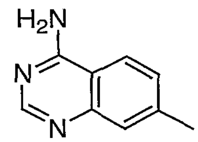
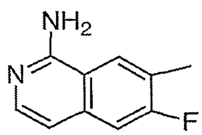
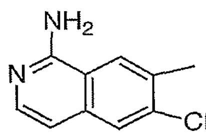
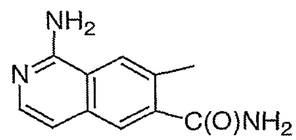
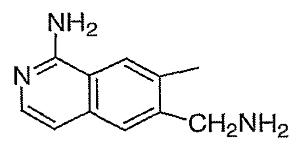
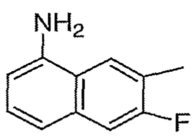
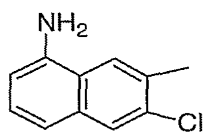
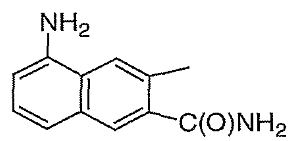
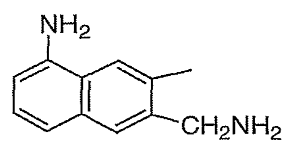
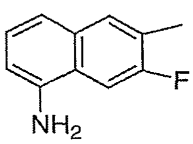
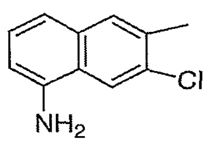
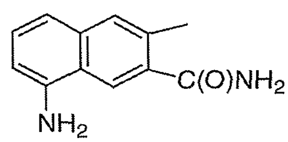
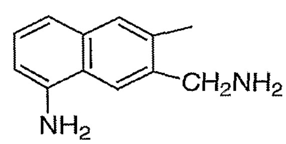
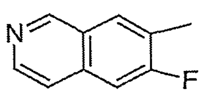
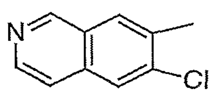
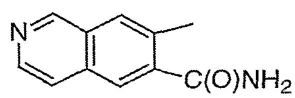
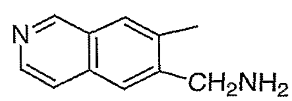
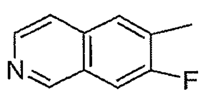
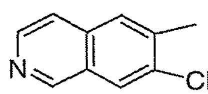
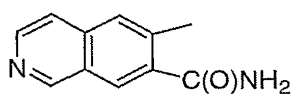
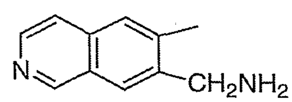
(b) Z is CH_2NH, $NHCH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$;

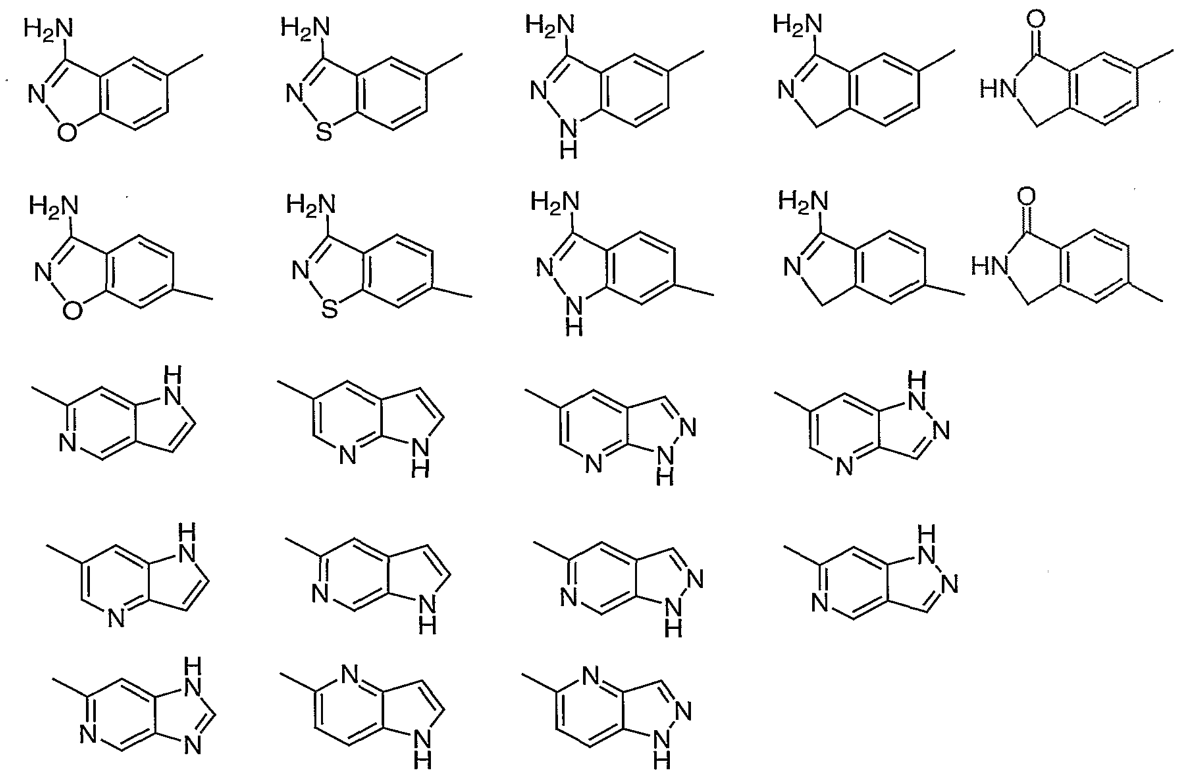
then Z^1 is other than $(CR^3R^{3a})_uNR^3(CH_2)_w$ and u+w is 1, 2, 3, or 4, $(CH_2)_uC(O)NR^3(CH_2)_w$, $(CR^3R^{3a})_uNR^3C(O)(CH_2)_w$, $(CH_2)_uS(O)NR^3(CH_2)_w$, $(CR^3R^{3a})_uS(O)_2NR^3(CH_2)_w$, or $(CH_2)_uNR^3S(O)_2(CH_2)_w$.

[3] In another preferred embodiment, the present invention provides a compound, wherein:

G is selected from the group: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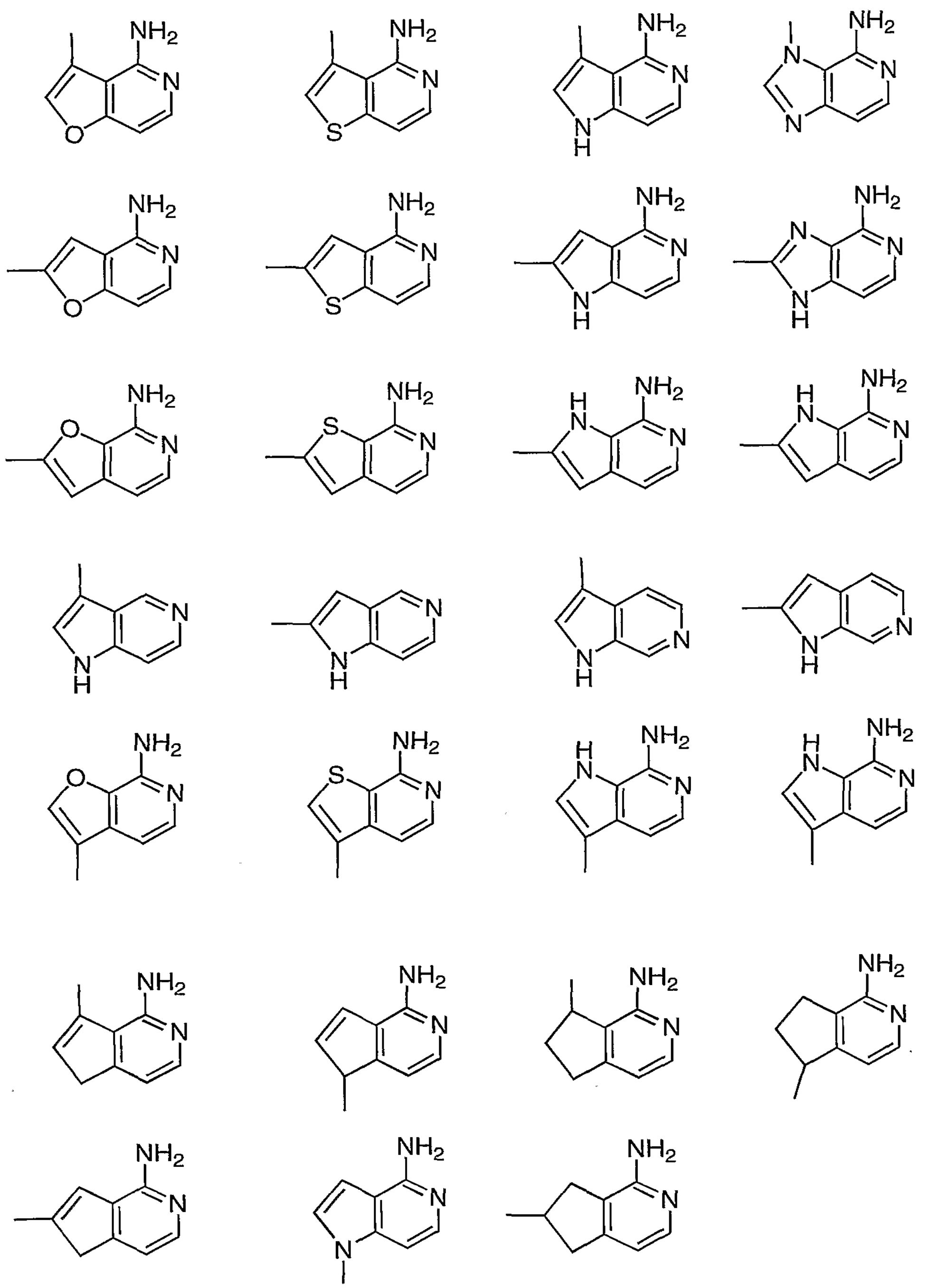
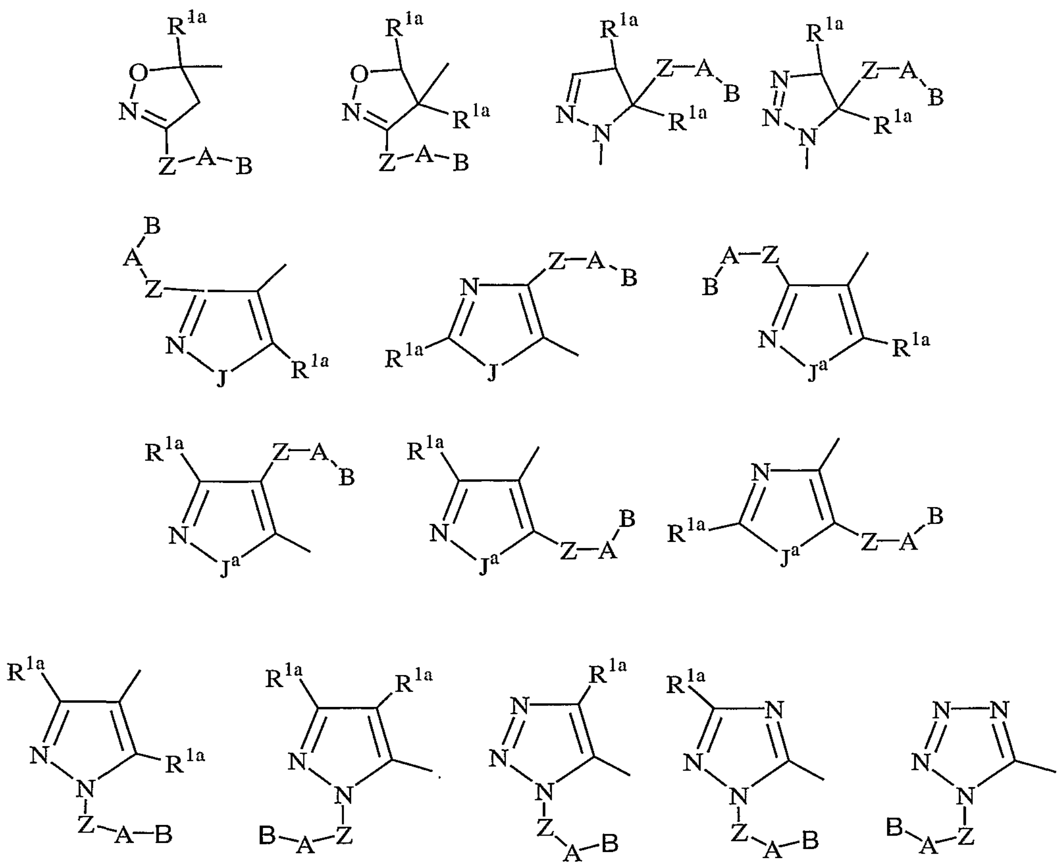


M-Z-A-B is selected from the group:



Y is selected from one of the following carbocyclic and heterocyclic rings that are substituted with 0-2 R^{4a};

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, 1,3,4-triazole, benzofuran, benzothiofuran, indole, benzimidazole, benzimidazolone, benzoxazole, benzthiazole, indazole, benzisoxazole, benzisothiazole, and isoindazole;

Z is selected from a bond, CH_2O, OCH_2, NH, CH_2NH, $NHCH_2$, $CH_2C(O)$, $C(O)CH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that Z does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $C(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, CF_3, 5-6 membered carbocycle substituted with 0-1 R^5, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5;

R^{4a}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, CF_3, F, Br, Cl, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $C(O)NHSO_2$-C_{1-4} alkyl, $S(O)_pR^5$, 5-6 membered carbocycle substituted with 0-1 R^5, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5;

alternatively, when

(a) B is other than an optionally substituted carbocycle; and,

(b) Z^1 is CH_2NH, $NHCH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, or $NHSO_2$;

then Z is other than CH_2NH, $NHCH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$

alternatively, when

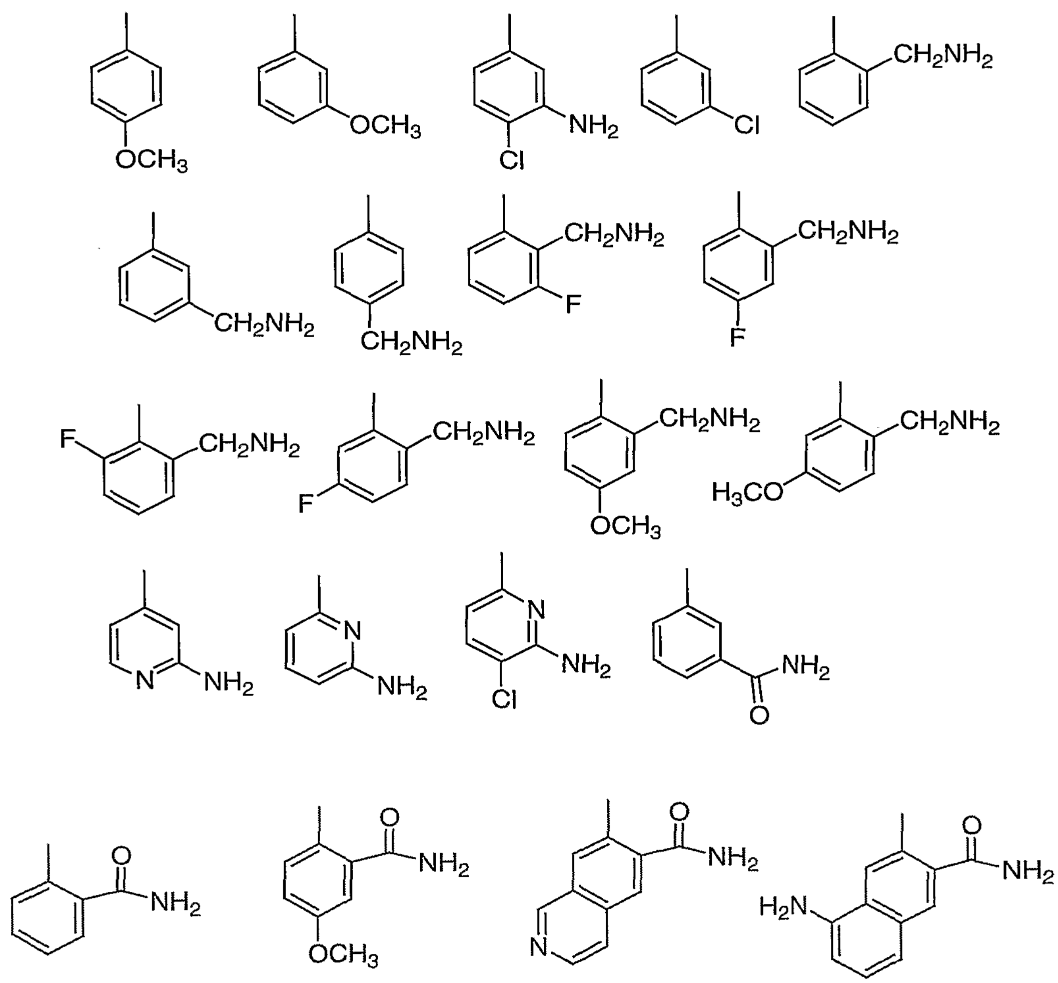
(a) B is other than an optionally substituted carbocycle; and,

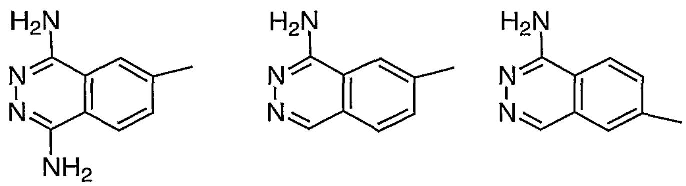
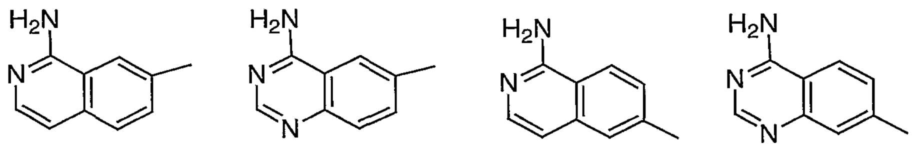
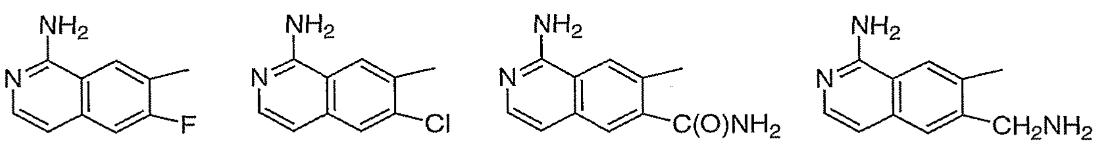
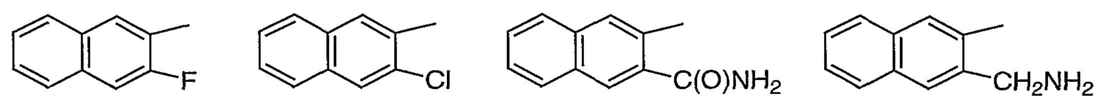
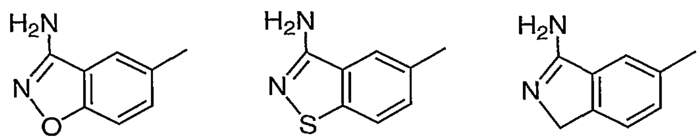
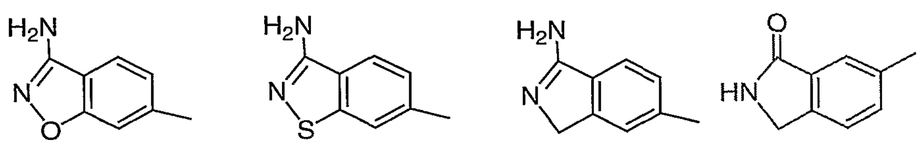
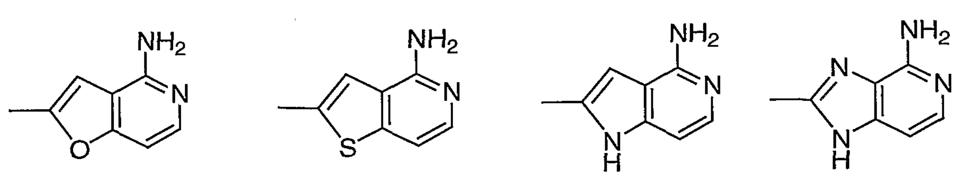
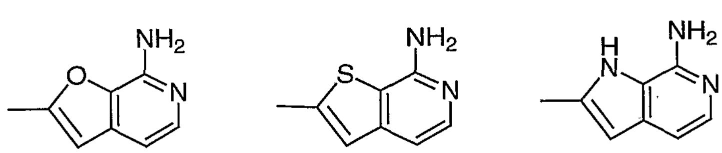
(b) Z is CH_2NH, $NHCH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$;

then Z^1 is other than CH_2NH, $NHCH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$.

[4] In another preferred embodiment, the present invention provides a compound, wherein:

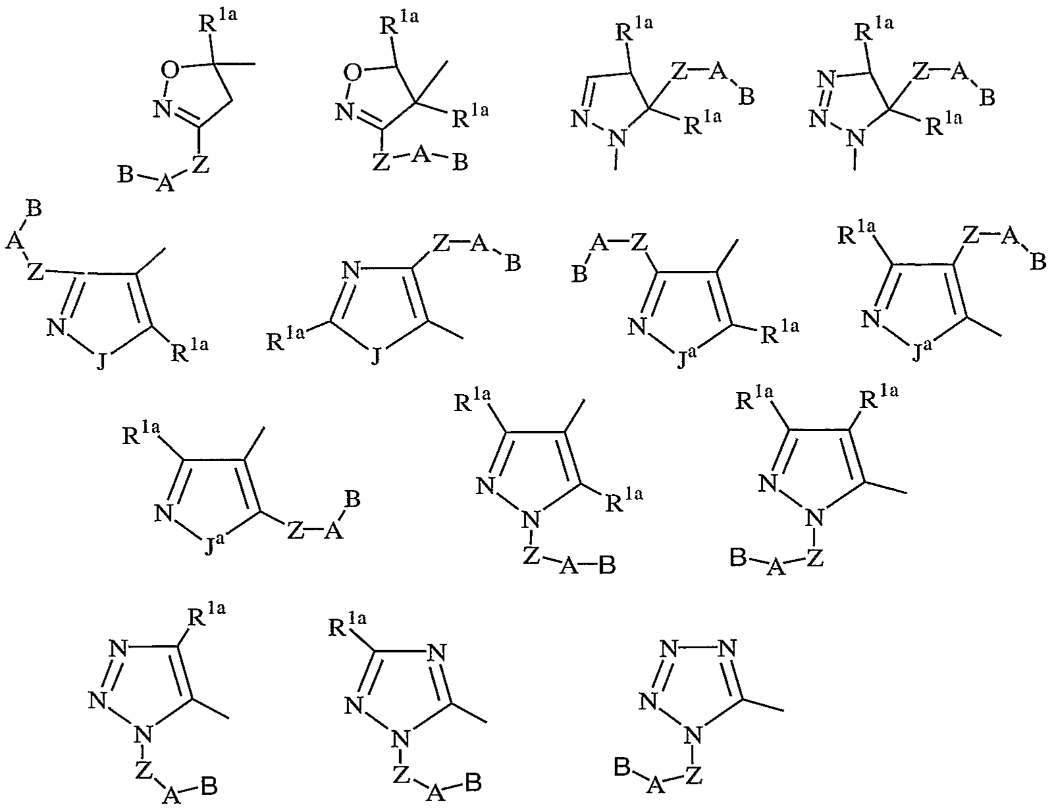
G is selected from:



;

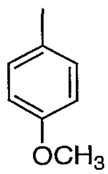
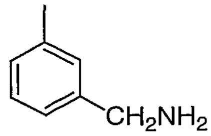
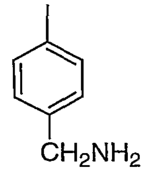
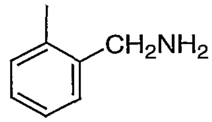
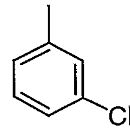
M-Z-A-B is selected from the group:

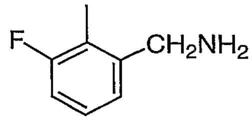
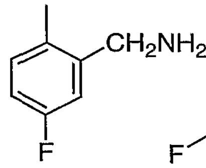
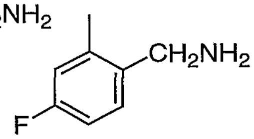
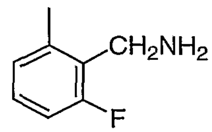


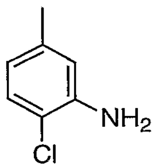
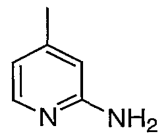
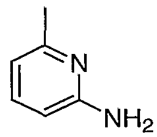
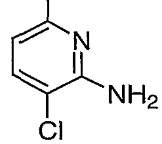
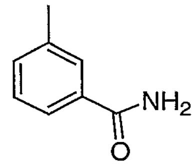
Z^1 is absent or is selected from CH_2, CH_2CH_2, CH_2O, OCH_2, NH, CH_2NH, $NHCH_2$, $CH_2C(O)$, $C(O)CH_2$, $C(O)NH$, $NHC(O)$, $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that G_1 does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached.

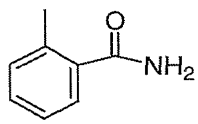
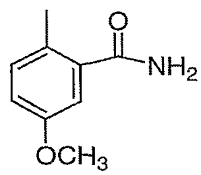
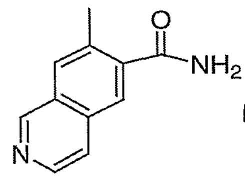
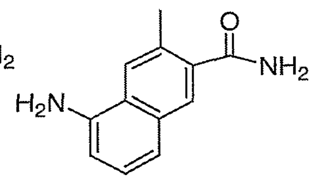
[5] In another preferred embodiment, the present invention provides a compound, wherein:

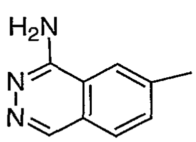
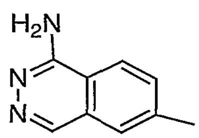
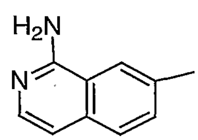
G is selected from:

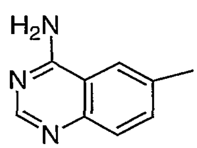
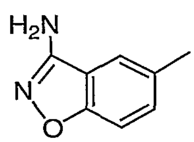
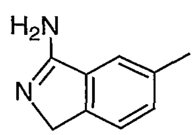
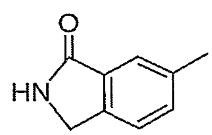
    

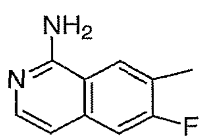
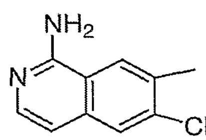
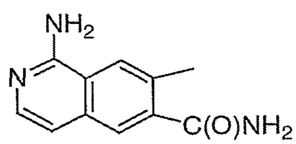
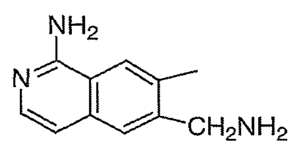
   

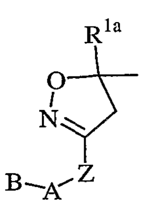
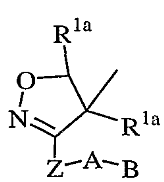
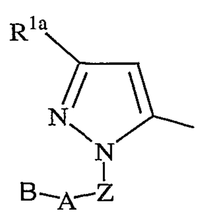
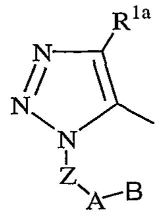
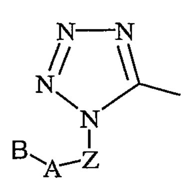
   

    ;

M-Z-A-B is selected from the group:

A is selected from phenyl, pyridyl, piperidinyl, and pyrimidyl, and is substituted with 0-2 R^4; and,

B is selected from phenyl, pyrrolidino, N-pyrrolidino-carbonyl, morpholino, N-morpholino-carbonyl, 1,2,3-triazolyl, imidazolyl, and benzimidazolyl, and is substituted with 0-1 R^{4a};

R^2, at each occurrence, is selected from H, CH_3, CH_2CH_3, cyclopropylmethyl, cyclobutyl, and cyclopentyl;

R^{2a}, at each occurrence, is H or CH_3, and CH_2CH_3;

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form pyrrolidine substituted with 0-2 R^{4b} or piperidine substituted with 0-2 R^{4b};

R^4, at each occurrence, is selected from OH, OR^2, $(CH_2)OR^2$, $(CH_2)_2OR^2$, F, Br, Cl, I, C_{1-4} alkyl, NR^2R^{2a}, $(CH_2)NR^2R^{2a}$, $(CH_2)_2NR^2R^{2a}$, CF_3, and $(CF_2)CF_3$;

R^{4a} is selected from C_{1-4} alkyl, CF_3, OR^2, $(CH_2)OR^2$, $(CH_2)_2OR^2$, NR^2R^{2a}, $(CH_2)NR^2R^{2a}$, $(CH_2)_2NR^2R^{2a}$, SR^5, $S(O)R^5$, $S(O)_2R^5$, $SO_2NR^2R^{2a}$, and 1-CF_3-tetrazol-2-yl;

R^{4b}, at each occurrence, is selected from H, CH_3, and OH;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl, and benzyl; and,

r, at each occurrence, is selected from 0, 1, and 2.

[6] In another preferred embodiment, the present invention provides a compound, wherein:

A is selected from the group: phenyl, piperidinyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

B is selected from the group: 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 2-(N,N-dimethylaminomethyl)phenyl, 2-(N-methylaminomethyl)phenyl, 2-(N-ethyl-N-methylaminomethyl)phenyl, 2-(N-pyrrolidinylmethyl)phenyl, 1-methyl-2-imidazolyl, 2-methyl-1-imidazolyl, 2-(dimethylaminomethyl)-1-imidazolyl, 2-(methylaminomethyl)-1-imidazolyl, 2-(N-(cyclopropylmethyl)aminomethyl)phenyl, 2-(N-(cyclobutyl)aminomethyl)phenyl, 2-(N-(cyclopentyl)aminomethyl)phenyl, 2-(N-(4-hydroxypiperidinyl)methyl)phenyl, and 2-(N-(3-hydroxypyrrolidinyl)methyl)phenyl.

[7] In another preferred embodiment, the present invention provides a compound selected from:

5-[(3-Amidinophenyl)aminocarbonyl]-3-[1,1′]-biphenyl-5-carbomethoxymethylisoxazoline;

5-[(3'-Aminobenzisoxazol-5'-yl))aminocarbonyl]-3-(2'-aminosulfonyl-[1,1']-biphenyl)isoxazoline;

5-Methyl-2-(2'-sulfamoyl-biphenyl-4-yl)-2H-pyrazole-3-carboxylic acid-(3-carbamimidoyl-phenyl)-amidine;

5-Methyl-2-(2'-sulfamoyl-biphenyl-4-yl)-2H-pyrazole-3-carboxylic acid (3-aminomethyl-phenyl)amide;

4-[(5-chloro-2-pyridinylamino)carbonyl]-1*H*-pyrazol-5-yl 1-isopropyl-4-piperidinecarboxamide;

1-(3-Amino-benzo[*d*]isoxazol-5-yl)-4-methyl-1*H*-pyrrole-2-carboxylic acid [4-(2-dimethylaminomethyl-imidazol-1-yl)-2-fluoro-phenyl]-amide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylthio-thiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylsulfoxide-thiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylsulfonyl-thiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-n-butylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-phenylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-isopropylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-propylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-ethylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-cyclopentylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-cyclobutylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-(3,4-difluorophenyl)thiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(3-Chlorophenylamino)carbonyl]-2-methylthio thiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylthio-thiazole-5-yl 4-(2'-N,N-dimethylaminomethyl phenyl)phenylcarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylthio-thiazole-5-yl 4-[2'-(4-hydroxypiperidylmethyl) phenyl]phenylcarboxamide;

3-[5-(2'-Methanesulfonylbiphenyl-4-carbonyl)-3-methylpyrazol-1-ylmethyl]benzamidine;

6-Methoxynaphthalene-2-carboxylic acid [1-(3-carbamimidoylbenzyl)-5-methyl-1*H*-pyrazol-3-ylmethyl]amide;

3-{5-Methyl-3-[(naphthalene-2-sulfonylamino)methyl]pyrazol-1-ylmethyl}benzamidine;

3-{3-[(6-Methoxynaphthalene-2-sulfonylamino)methyl-5-methylpyrazol-1-ylmethyl}benzamidine;

3-{3-[(7-Chloronaphthalene-2-sulfonylamino)methyl]pyrazol-1-ylmethyl}benzamidine;

3-{3-[(7-Methoxynaphthalene-2-sulfonylamino)methyl]pyrazol-1-ylmethyl}benzamidine;

1-Isopropylpiperidine-4-carboxylic acid [4-(4-chlorobenzoylamino)furazan-3-yl]amide;

1-Isopropylpiperidine-4-carboxylic acid [5-(4-chlorobenzoylamino)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]amide;

1-Isopropylpiperidine-4-carboxylic acid [4-(5-chloropyridin-2-ylcarbamoyl)-2-methyl-2*H*-pyrazol-3-yl]amide;

1-Isopropylpiperidine-4-carboxylic acid [4-(5-chloropyridin-2-ylcarbamoyl)-2-phenyl-2*H*-pyrazol-3-yl]amide; and,

1-Isopropylpiperidine-4-carboxylic acid [4-(5-chloropyridin-2-ylcarbamoyl)-3-methylisothiazol-5-yl]amide;

or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel compound wherein A is selected from one of the following carbocyclic and heterocyclic systems that are substituted with 0-2 R^4;

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

In another embodiment, the present invention provides a novel compound wherein A is selected from phenyl, piperidinyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R^4.

In another embodiment, the present invention provides a novel compound wherein A is selected from the group: phenyl, piperidinyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl,

3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl.

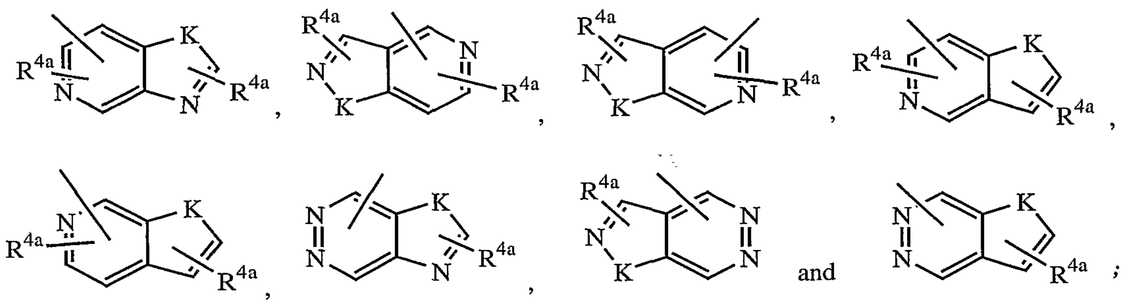
In another embodiment, the present invention provides a novel compound wherein:

B is selected from: H, Y, and X-Y, provided that Z and B are attached to different atoms on A;

X is selected from $-(CR^2R^{2a})_{1-4}-$, $-C(O)-$, $-C(=NR^{1c})-$, $-CR^2(NR^{1c}R^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)NR^2-$, $-NR^2-$, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

Y is selected from one of the following carbocyclic and heterocyclic systems that are substituted with 0-2 R^{4a};
cyclopropyl, cyclopentyl, cyclohexyl, phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

alternatively, Y is selected from the following bicyclic heteroaryl ring systems:



K is selected from O, S, NH, and N.

In another embodiment, the present invention provides a novel compound wherein:

Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, 1,3,4-triazole, benzofuran, benzothiofuran, indole, benzimidazole, benzimidazolone, benzoxazole, benzthiazole, indazole, benzisoxazole, benzisothiazole, and isoindazole.

In another embodiment, the present invention provides a novel compound wherein B is selected from phenyl,

pyrrolidino, N-pyrrolidino-carbonyl, morpholino, N-morpholino-carbonyl, 1,2,3-triazolyl, imidazolyl, and benzimidazolyl, and is substituted with 0-1 R^{4a}.

In another embodiment, the present invention provides a novel compound wherein B is selected from the group: 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 2-(N,N-dimethylaminomethyl)phenyl, 2-(N-methylaminomethyl)phenyl, 2-(N-ethyl-N-methylaminomethyl)phenyl, 2-(N-pyrrolidinylmethyl)phenyl, 1-methyl-2-imidazolyl, 2-methyl-1-imidazolyl, 2-(dimethylaminomethyl)-1-imidazolyl, 2-(methylaminomethyl)-1-imidazolyl, 2-(N-(cyclopropylmethyl)aminomethyl)phenyl, 2-(N-(cyclobutyl)aminomethyl)phenyl, 2-(N-(cyclopentyl)aminomethyl)phenyl, 2-(N-(4-hydroxypiperidinyl)methyl)phenyl, and 2-(N-(3-hydroxypyrrolidinyl)methyl)phenyl.

In another embodiment, the present invention provides a novel compound wherein:

G is a group of formula IIa or IIb:

IIa IIb

ring D, including the two atoms of Ring E to which it is attached, is a 5-6 membered non-aromatic ring consisting of carbon atoms, 0-1 double bonds, 0-1 $S(O)_p$, or O, and 0-2 N, and D is substituted with 0-2 R;

alternatively, ring D, including the two atoms of Ring E to which it is attached, is a 5-6 membered aromatic system consisting of carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, and D is substituted with 0-2 R;

E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, and is substituted with 0-2 R;

R is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl$)_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl$)_2$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3;

alternatively, the bridging portion of ring D is absent, and ring E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, and ring E is substituted with R^a and R^b;

R^a is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl$)_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl$)_2$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3;

R^b is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$

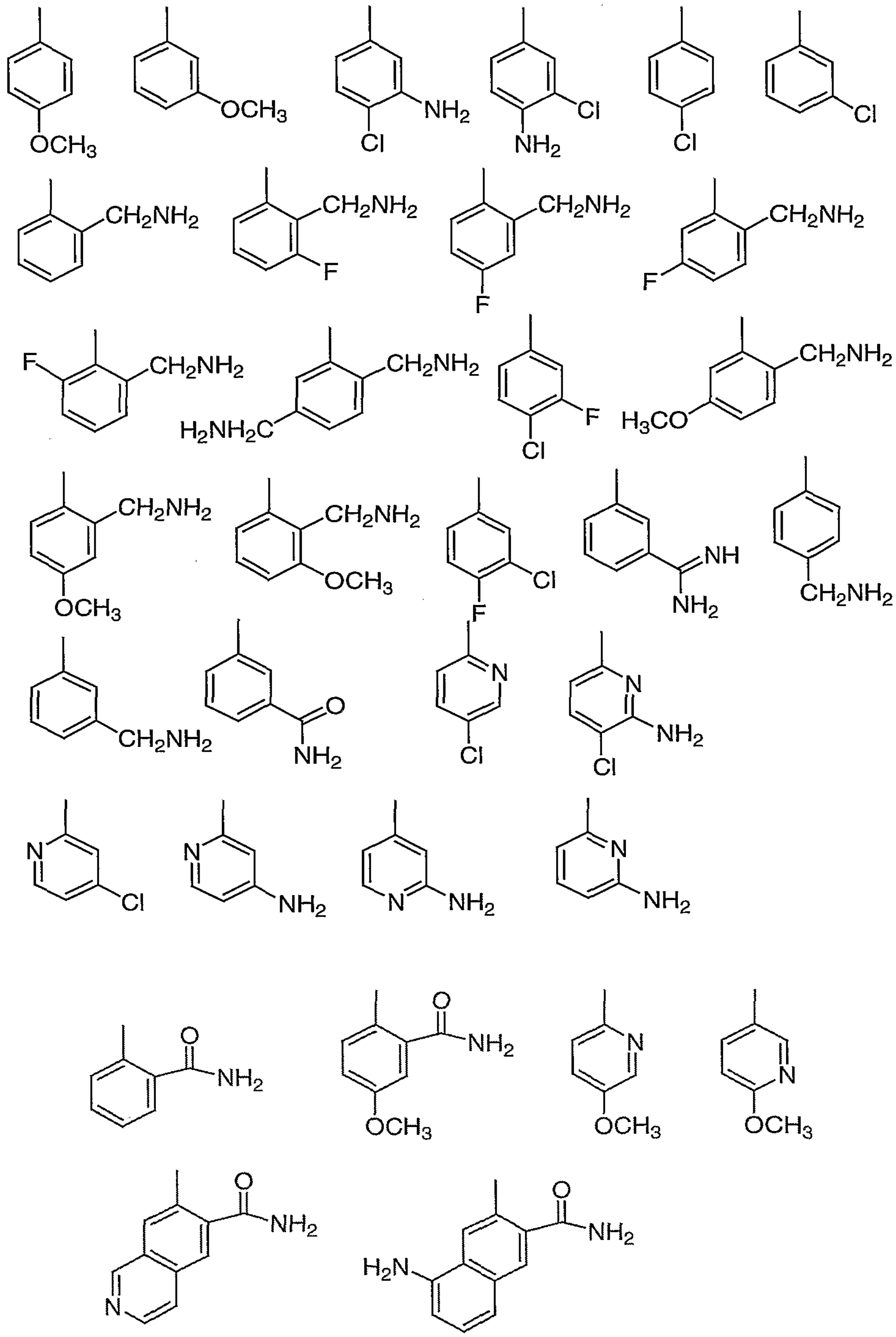
alkyl)$_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl)$_2$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3;

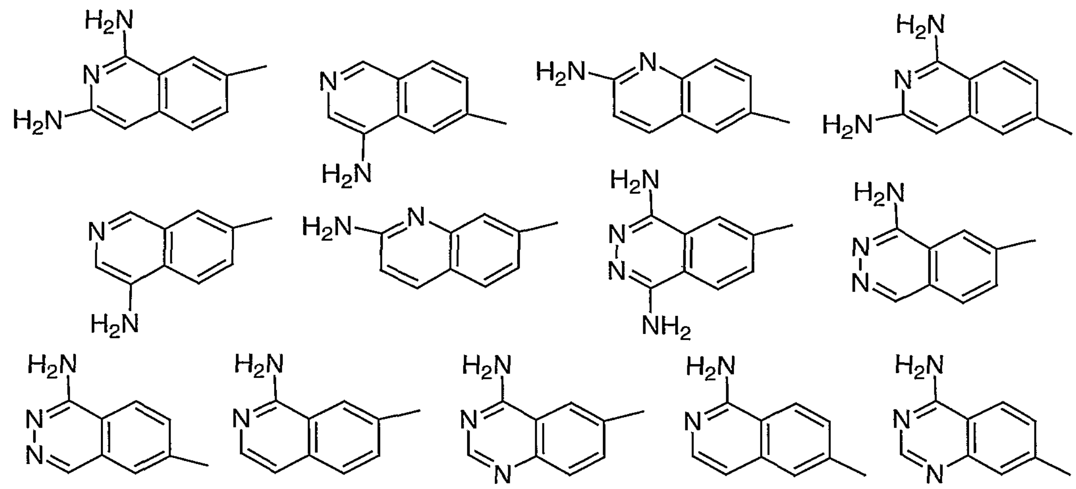
alternatively, R^a and R^b combine to form methylenedioxy or ethylenedioxy;

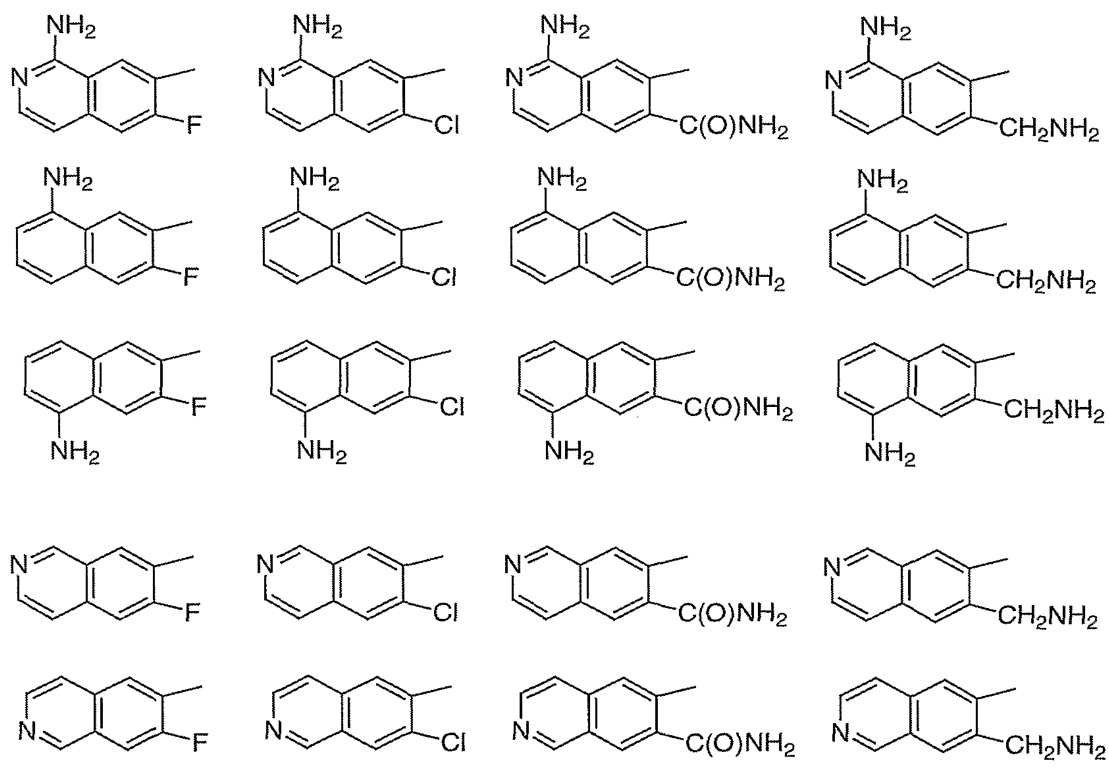
alternatively, the bridging portion of ring D is absent, and ring E is selected from pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, triazolyl, thiophenyl, and thiazolyl, and ring E is substituted with 0-2 R^c;

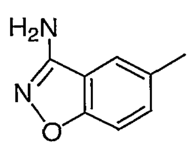
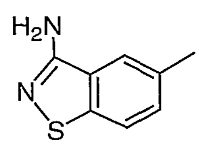
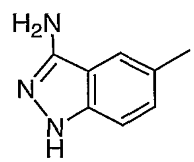
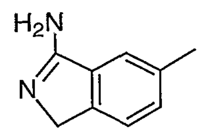
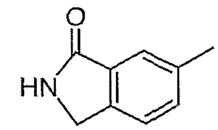
R^c is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl)$_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl)$_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl)$_2$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3.

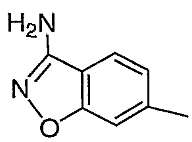
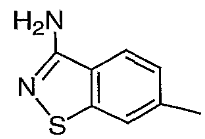
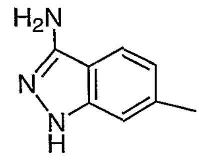
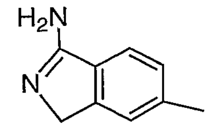
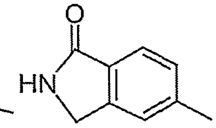
In another embodiment, the present invention provides a novel compound wherein G is selected from the group:

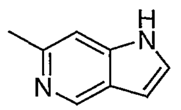
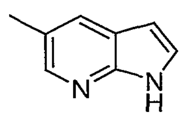
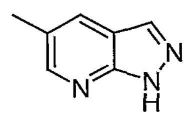
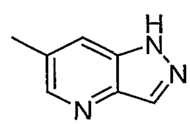


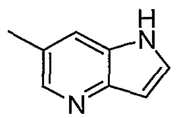
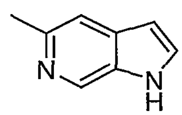
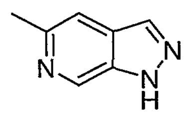
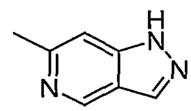


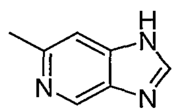
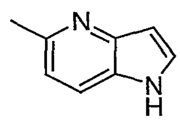
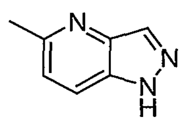


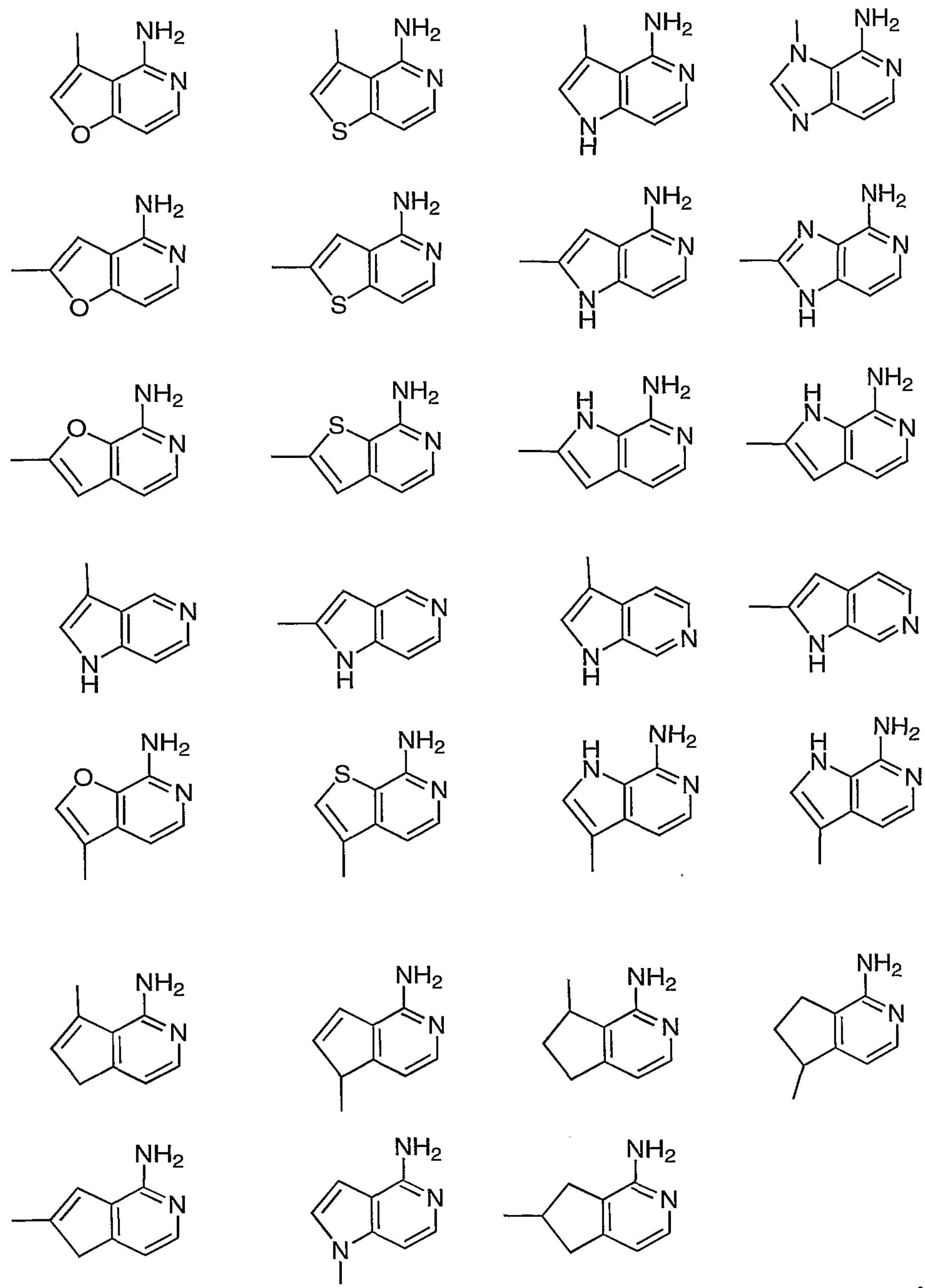
    

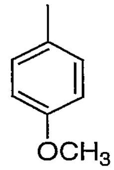
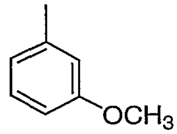
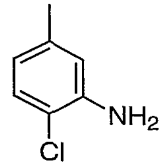
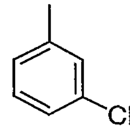
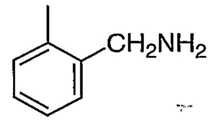
   

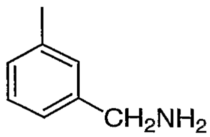
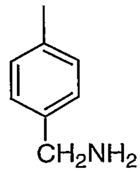
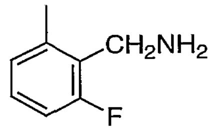
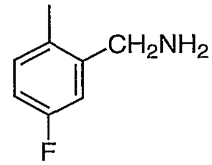
   

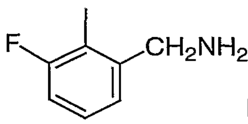
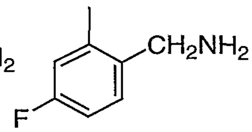
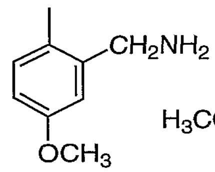
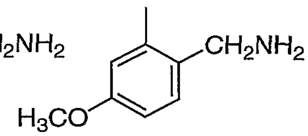
  

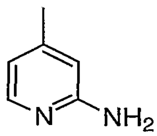
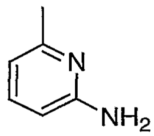
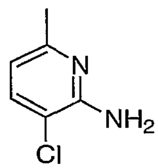
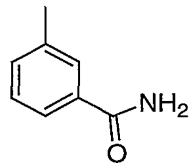


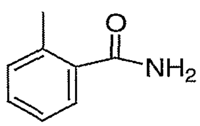
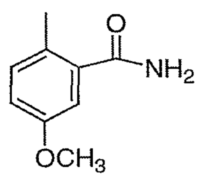
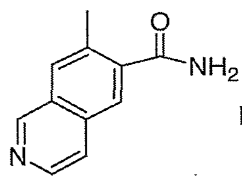
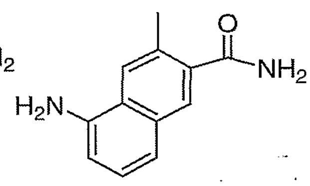
In another embodiment, the present invention provides a novel compound wherein G is selected from the group:

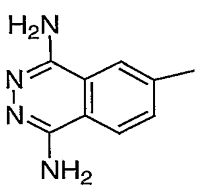
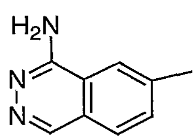
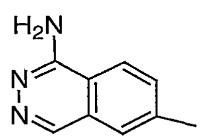
    

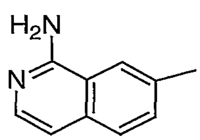
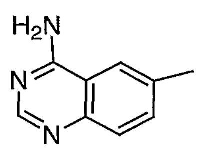
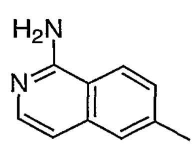
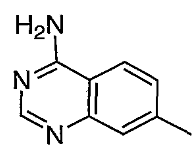
   

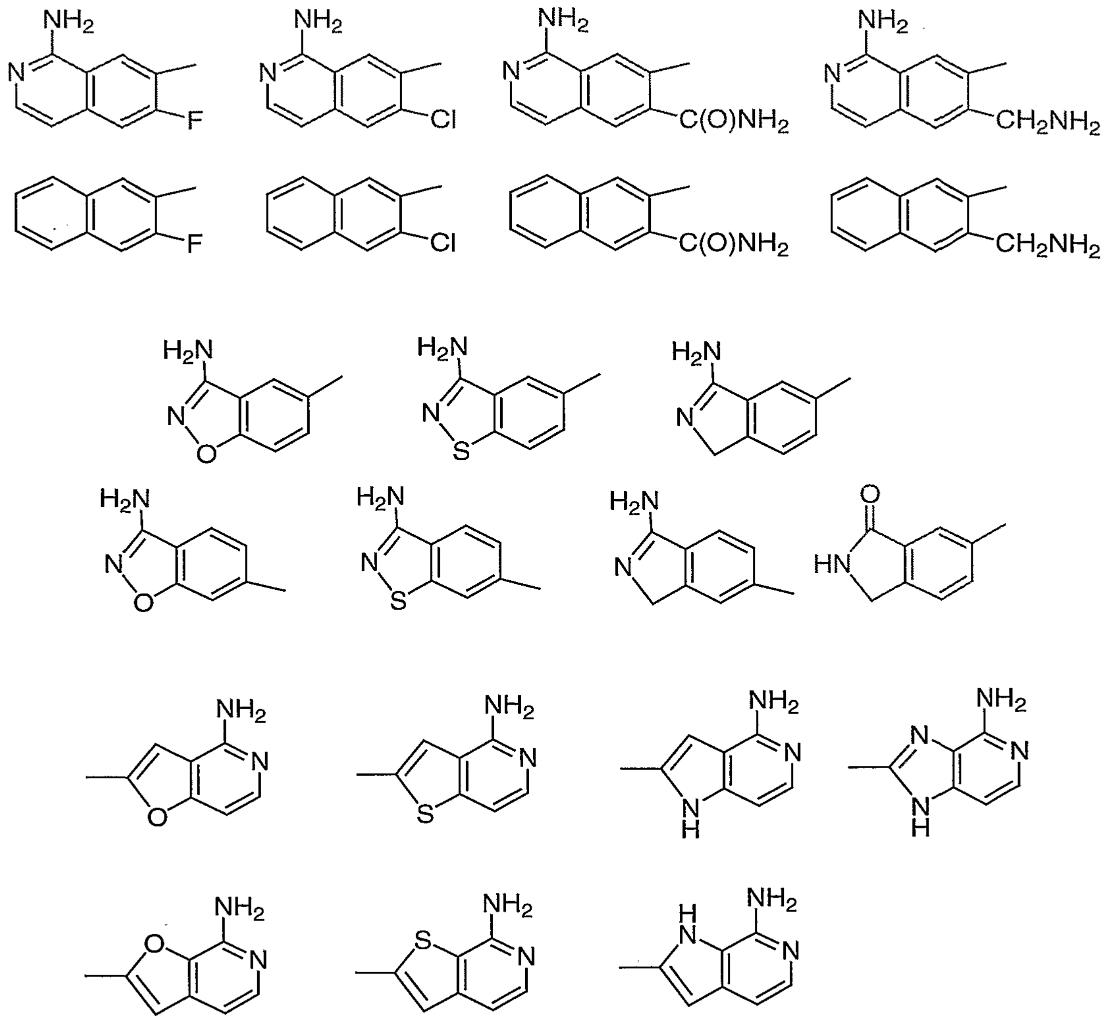
   

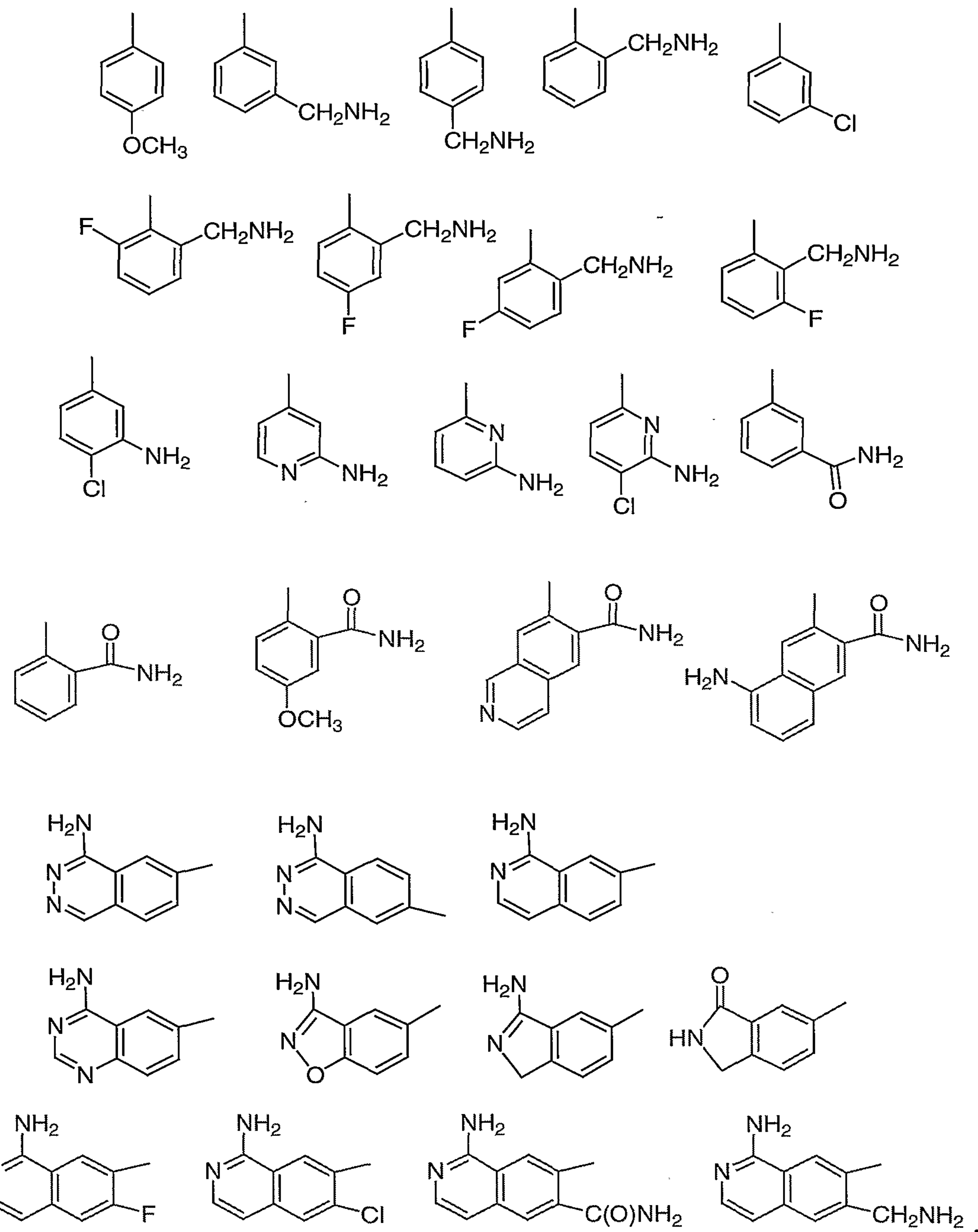
   



In another embodiment, the present invention provides a novel compound wherein G is selected from the group:



In another embodiment, the present invention provides novel pharmaceutical compositions, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method for treating or preventing a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides novel compounds as described above for use in therapy.

In another embodiment, the present invention provides the use of novel compounds as described above for the manufacture of a medicament for the treatment of a thromboembolic disorder.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric,

racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. Tautomers of compounds shown or described herein are considered to be part of the present invention.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substitent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

When any variable (e.g., R^6) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^6, then said group may optionally be substituted with up to two R^6 groups and R^6 at each occurrence is selected independently from the definition of R^6. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

One of ordinary skill in the art would recognize that a wide range of molecular weights are possible depending on the variables chosen. One of ordinary skill in the pharmaceutical art would recognize that the higher the molecule weight of a drug, the more difficult it is to manufacture and administer. Therefore, the molecular weights of the compounds of the present invention are preferably less than 1000 grams per mole. More preferably, the molecular weights are less than 950, 900, 850, 800, 750, 700, 650, 600, 550, or 500 grams per mole.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. C_{1-6} alkyl, is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents an alkyl group as

defined above with the indicated number of carbon atoms attached through an oxygen bridge. C_{1-6} alkoxy, is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. C_{3-7} cycloalkyl, is intended to include C_3, C_4, C_5, C_6, and C_7 cycloalkyl groups. Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl. C_{2-10} alkenyl, is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. "Alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl and propynyl. C_{2-6} alkynyl, is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

As used herein, "carbocycle" or "carbocyclic group" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane,

[2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl.

As used herein, the term "heterocycle" or "heterocyclic group" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic ring that is saturated, partially unsaturated or unsaturated (aromatic), and that consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, NH, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic aromatic ring that consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, NH, O and S. It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl,

benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound

medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate,

ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc...) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Substituted" is intended to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O) group, then 2 hydrogens on the atom are replaced.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention or an amount of the combination of compounds claimed effective to inhibit factor Xa. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, *Adv. Enzyme Regul.* **1984**, *22*, 27-55, occurs when the effect (in this case, inhibition of factor Xa) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antiviral effect, or some other beneficial effect of the combination compared with the individual components.

SYNTHESIS

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent appropriate to the

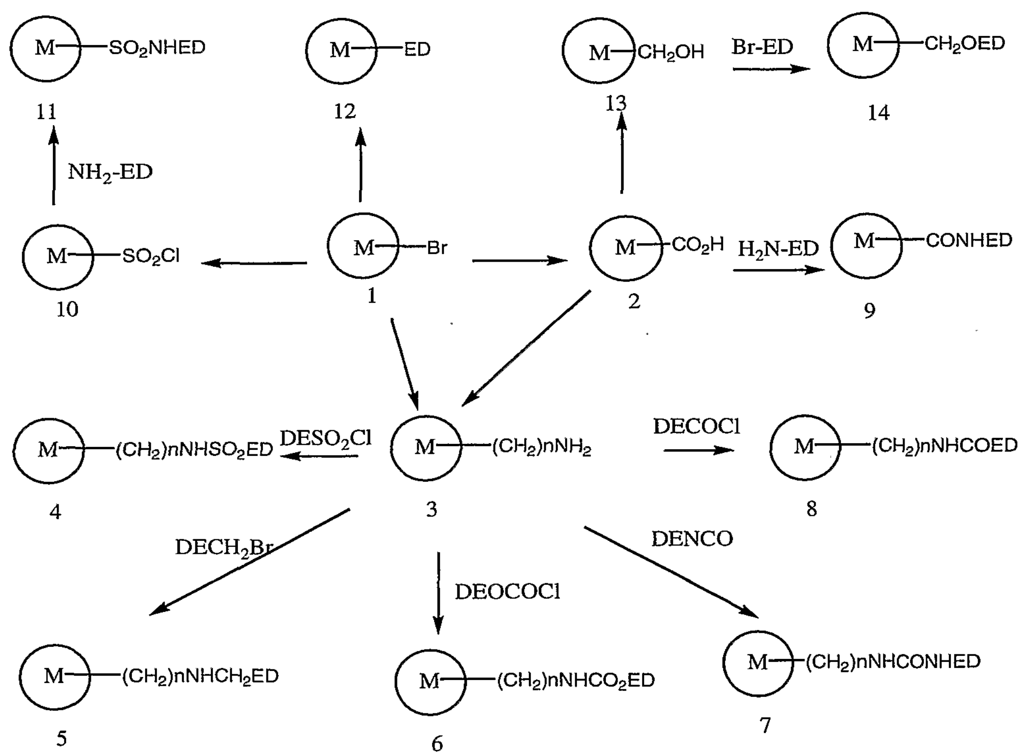
reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometime require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting groups present in the compounds described in the invention. An authoritative account described the many alternatives to the trained practitioner is Greene and Wuts (Protective Groups in Organic Synthesis, Wiley and Sons, 1991). All references cited herein are hereby incorporated in their entirety herein by reference.

The compounds of the present invention have a group "G" (i.e., D-E) attached to Z_1-M. Preparations of the group "D-E" can follow the same methods described in WO98/28269, WO98/57951, and WO98/57937, the contents of which are incorporated herein by reference. Preparations of the M and the "Z-A-B" moieties within "M" can follow the same methods described in WO97/23212, WO97/30971, WO97/38984, WO98/01428, WO98/06694, WO98/28269, WO98/28282, WO98/57934, WO98/57937, and WO98/57951, the contents of which are incorporated herein by reference.

A general synthesis of the compounds of this invention is shown in Scheme 1. Appropriately substituted "M" such as **1** and **2** can be prepared by the methods described in the references shown above. Alternately, **2** can be prepared from **1** or vice versa. Both compounds **1** and **2** can be converted to compound **3**. Reaction of **3** with various functionalities

containing "ED" will provide sulfonamide **4**, amine **5**, carbamate **6**, urea **7**, and amide **8**. Reaction of carboxylic acid **2** with "$DENH_2$" gives amide **9**. The sulfonyl chloride **10** can be prepared from the bromide **1** and then reacted with "$DENH_2$" to give sulfonamide **11**. Compound **12** with "ED" directly linked to "M" can be prepared from bromide **1** via Ullmann or Suzuki reaction. Compound **14** with an ether linkage can be prepared from **13**, which in turn can be obtained from acid **2**.

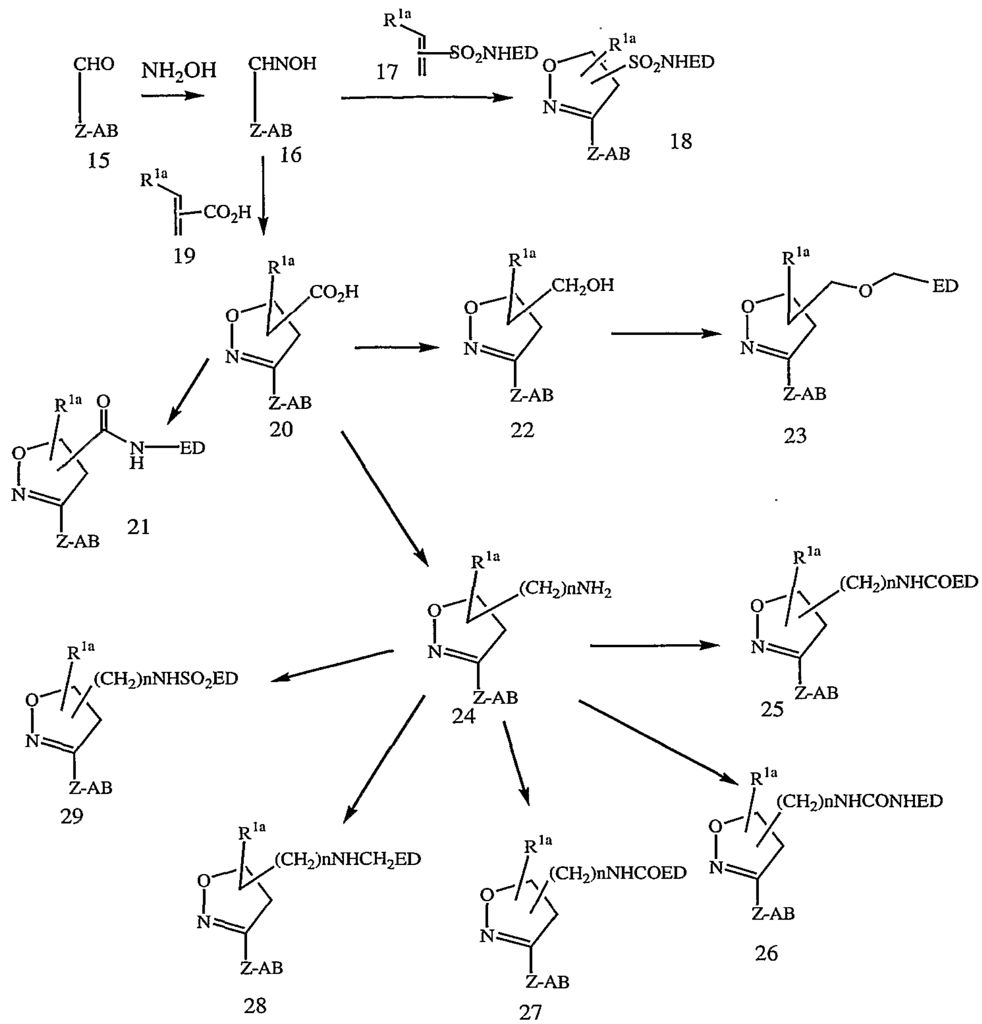
Scheme 1



Scheme 2 shows a general synthesis of isoxazolines. An appropriately substituted aldehyde **15** is reacted with hydroxylamine to give the corresponding oxime **16**. The oxime **16** is then oxidatively chlorinated and dehydrochlorinated. The resulting nitrile oxide is trapped by a suitable alkene under phase transfer conditions according to the method of

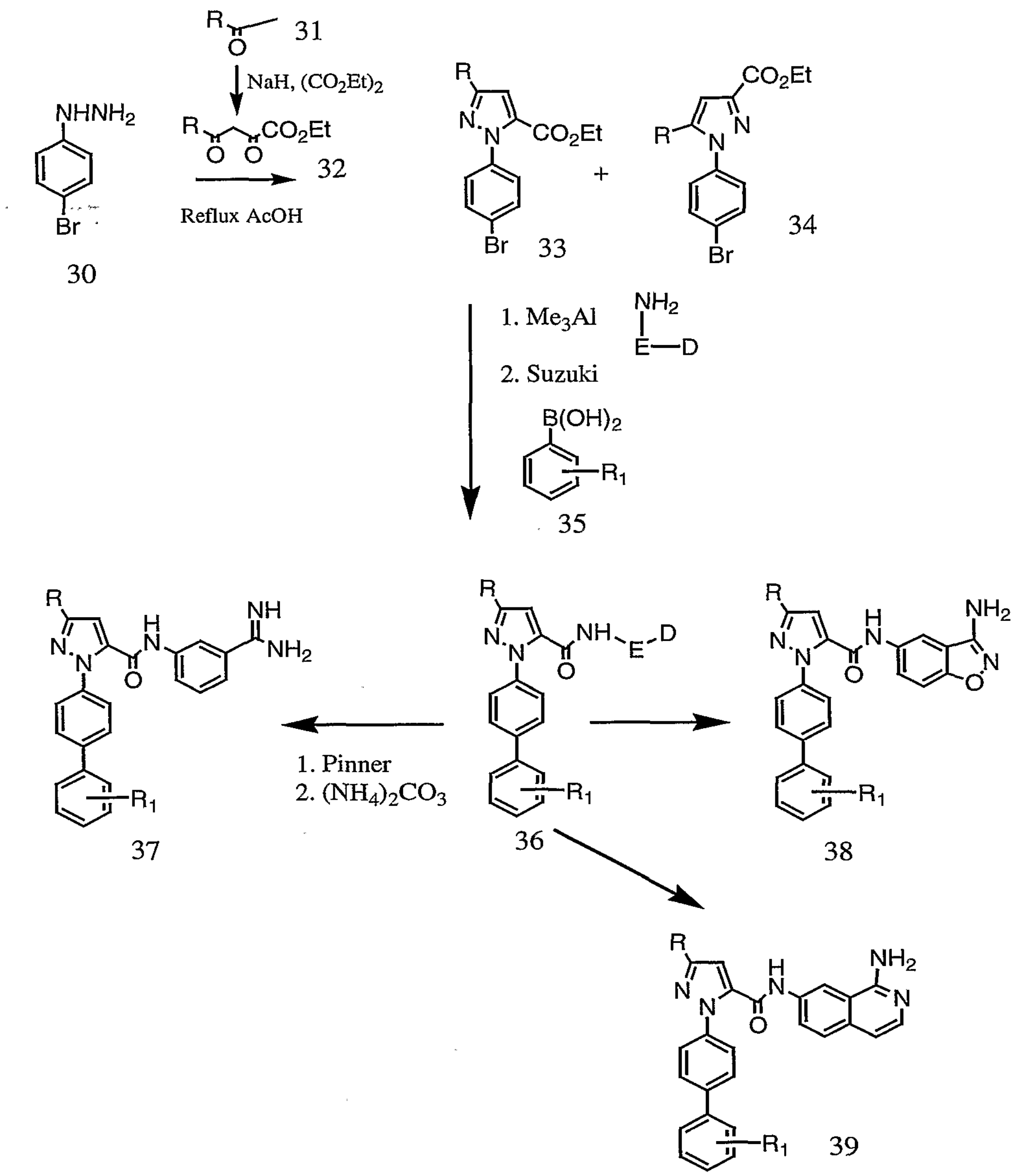
Lee (*Synthesis* **1982**, 508). Alternatively, an appropriately substituted hydroxylamine is treated with NCS in DMF according to the method of Liu, et al. (*J. Org. Chem.* **1980**, *45*, 3916). The resulting hydroximinoyl chloride is then dehydrohalogenated in situ using TEA to give a nitrile oxide, which undergoes a 1,3-dipolar cycloaddition with a suitably substituted alkene to afford the isoxazolines **18** and **20**. A mixture of regioisomers is formed and the regioisomers can be separated by column chromatography. Optically active isoxazolines can be obtained by chiral HPLC separation of the two enantiomers or enzymatic resolution of the regioisomeric esters. It can also be obtained by the use of an appropriate chiral auxilliary on the dipolarophile as described by Olsson (*J. Org. Chem.* 1988, *53*, 2468). Substituted alkenes **17** and **19** with various R^{1a} groups can be prepared by the same methods described in U.S. Patent No. 5,939,418; the contents of which are incorporated herein by reference. Isoxazolin-5-yl carboxylic acids can be coupled to "DE-NH_2" using standard conditions to give amide **21**. Carboxylic acid **20** can be reduced to alcohol **22**, which is then converted to ether **23** by reaction with "Br-ED". Carboxylic acid **20** can also be converted to amine **24** by Curtis rearrangement or reduction followed by amination. Amine 24 can then reacted with various functionalities containing "ED" to provide amide **25**, urea **26**, carbamate **27**, amine **28**, and sulfonamide **29**.

Scheme 2



Pyrazoles of this invention is where Z_1 is an amide is exemplified in Scheme 3. Compounds of this invention wherein the Z_1 group is other than an amide can be easily manipulated to other linker functionalities as shown in Scheme 1-2 according to the methodologies known in the art, including the methodologies outlined in WO98/28269 and WO98/28282, the contents of both are incorporated herein in their entirety. Alternatively pyrazoles, thiazoles, and other heterocycles can easily be prepared according to methods outlined in Scheme 4 and 5.

Scheme 3


NaH, $(CO_2Et)_2$
Reflux AcOH
1. Me_3Al
2. Suzuki
1. Pinner
2. $(NH_4)_2CO_3$
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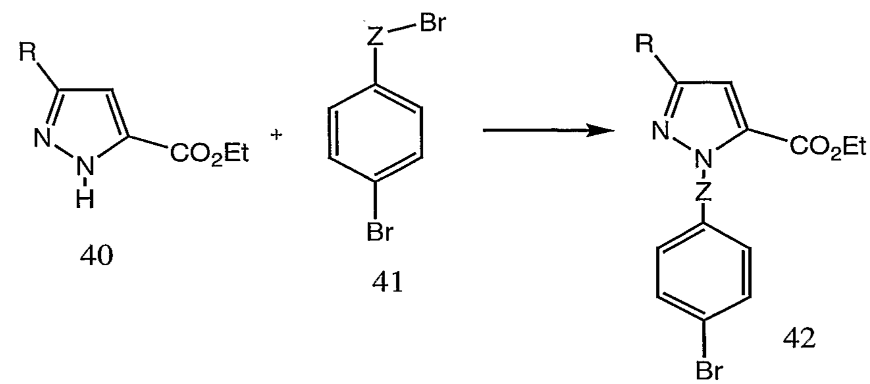
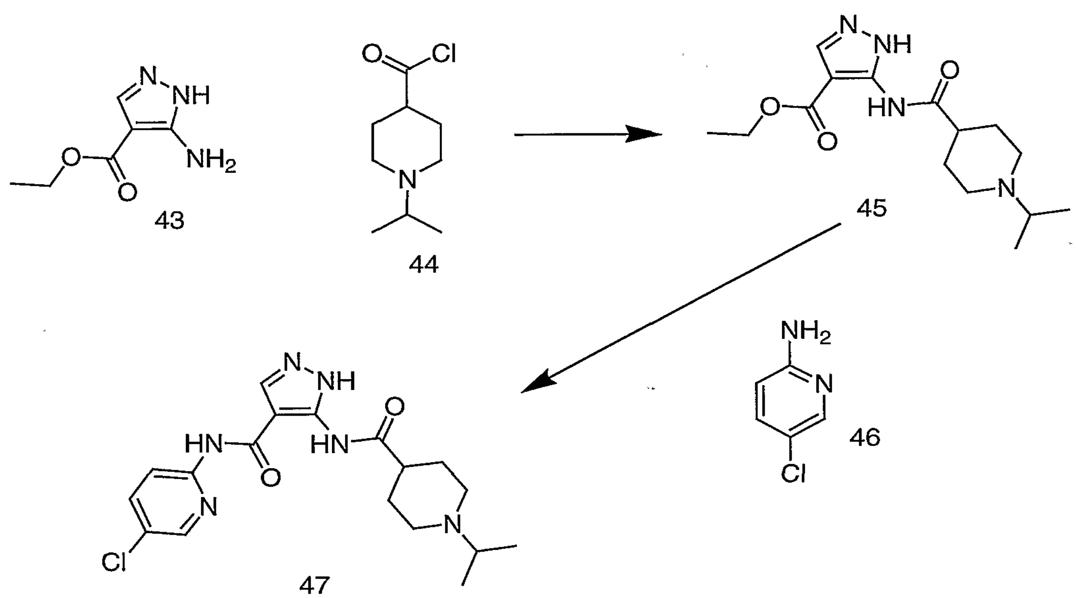
Scheme 4



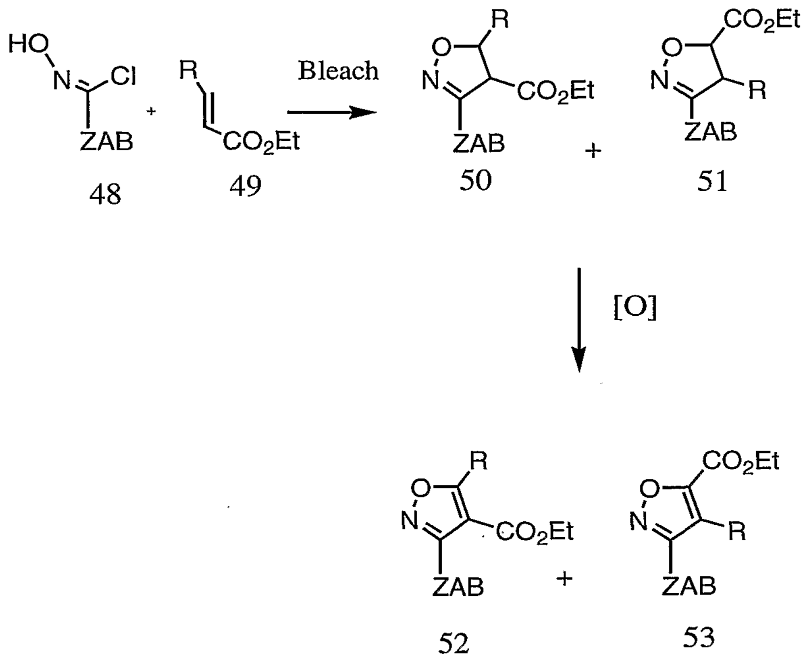
Scheme 5



Compounds of this invention wherein the M group is a 1,2,3-triazole, 1,2,4-triazole, imidazoles and other nitrogen based five membered heterocycles can be prepared according to the methodologies outlined in WO98/28269.

Isoxazolines and isoxazoles of this invention can be prepared according to the methods outlined in Scheme 6. Further elaborations according to methods outlined in Scheme 1-5 afford compounds of this invention.

Scheme 6



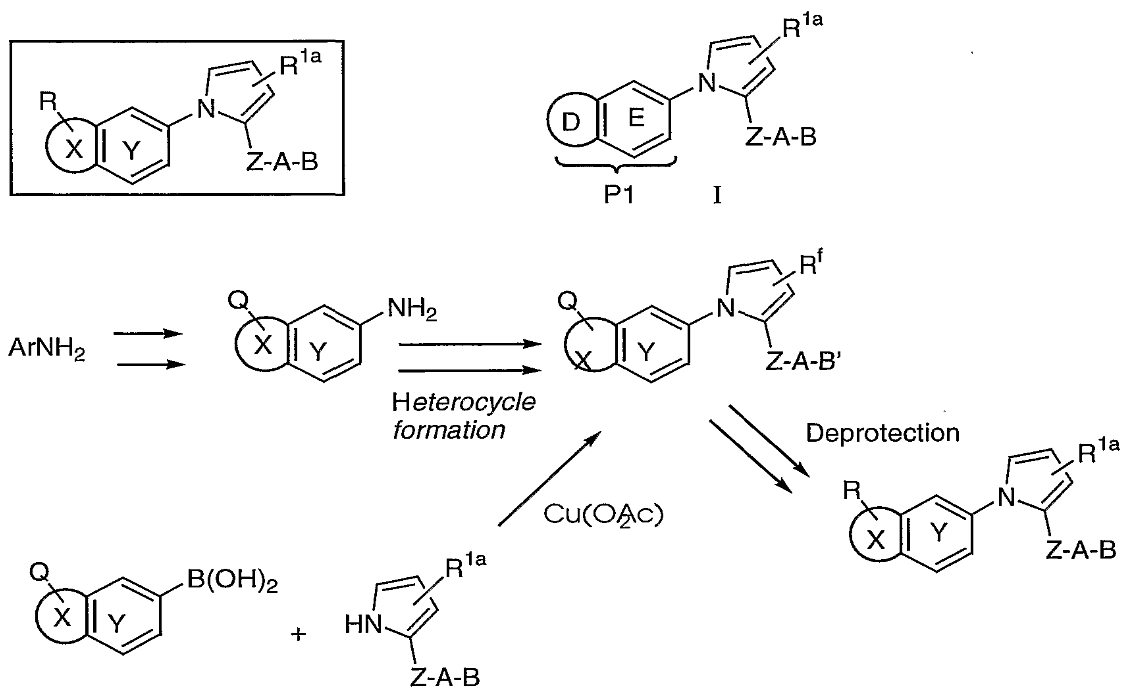
Thiazoles, oxazoles and other carbon based five membered heterocycles of this invention can be prepared according to the methodologies outlined in WO98/28269. Further elaborations according to the methodologies outlined in Scheme 1-5 can afford compounds of the present invention.

One general synthesis of compounds of Formula I where ring M is N-linked is shown in Scheme 7a. This scheme and those following typically exemplify pyrrole. However, one of ordinary skill in the art would recognize that the other heterocycles of the present invention could be prepared in a like manner.

Q, B′ and R^f are protected functional groups that can be converted to R, B and R^{1a} respectively. D-E can also be called P1, the sidechain that fits into the S1 pocket of fXa. The compounds can also be obtained by changing the sequences of the reaction steps as described in Scheme 7a. For N-linked M ring, the appropriate heterocyclic aniline is treated under conditions described in "The Chemistry of

Heterocyclic Compounds, Weissberger, A. and Taylor, E. C. Ed., John Wiley & Sons" or as described later in the synthesis section to give N-linked ring M. Further modifications and deprotections give N-linked ring M with R, Z-A-B and R^{1a} substitutents. Alternatively, the corresponding arylboronic acid can arylate a properly substituted pyrrole under copper-promoted C-N coupling conditions.

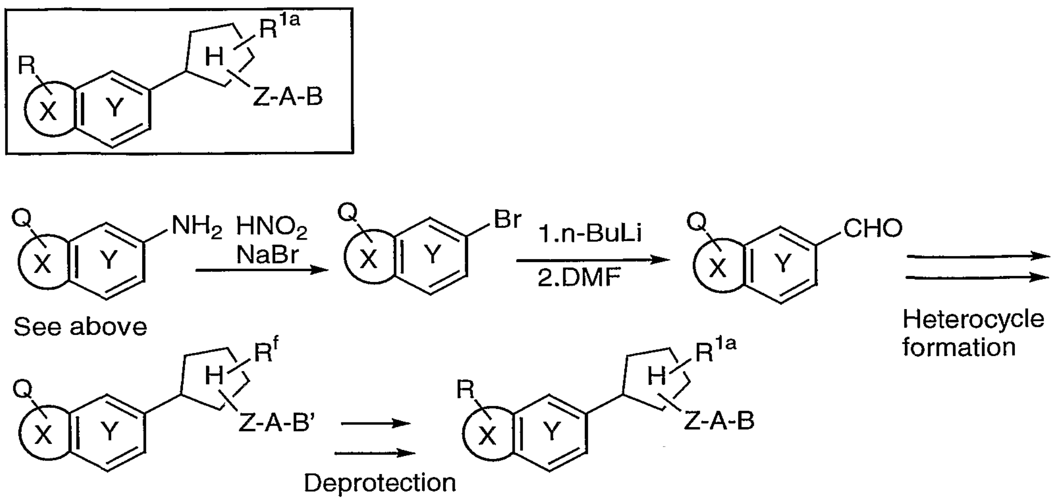
Scheme 7a



In Scheme 7b is shown how to obtain compounds wherein the pyrrole is C-linked. The aniline from Scheme 7a is diazotized with nitrous acid and treated with NaBr to give the heterocyclic bromide. Treatment with n-BuLi followed by DMF gives an aldehyde which can be converted to ring M as described in "The Chemistry of Heterocyclic Compounds, Weissberger, A. and Taylor, E. C. Ed., John Wiley & Sons" or as will be described. Other precursor functional groups

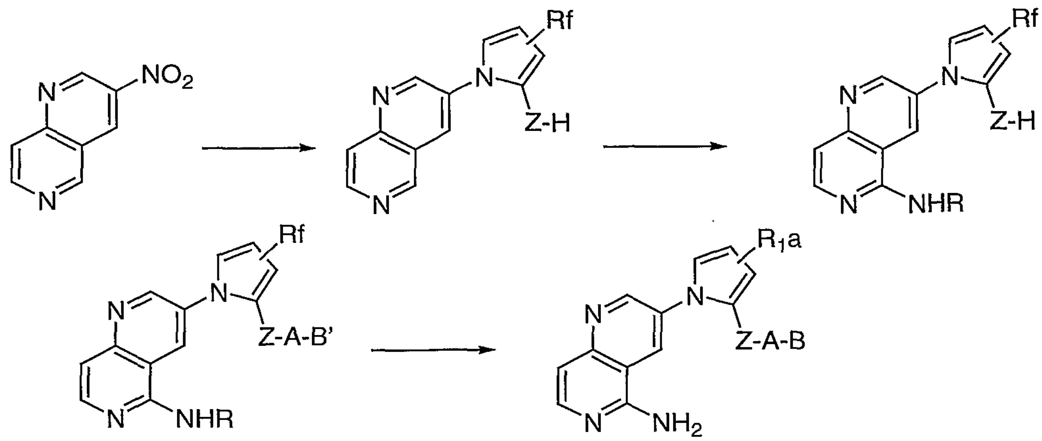
like acid, cyanide, methylketone, etc. can also be used to form the ring M. Further modifications and deprotections can yield a pyrrole substituted with R, Z-A-B and R^{1a}.

Scheme 7b



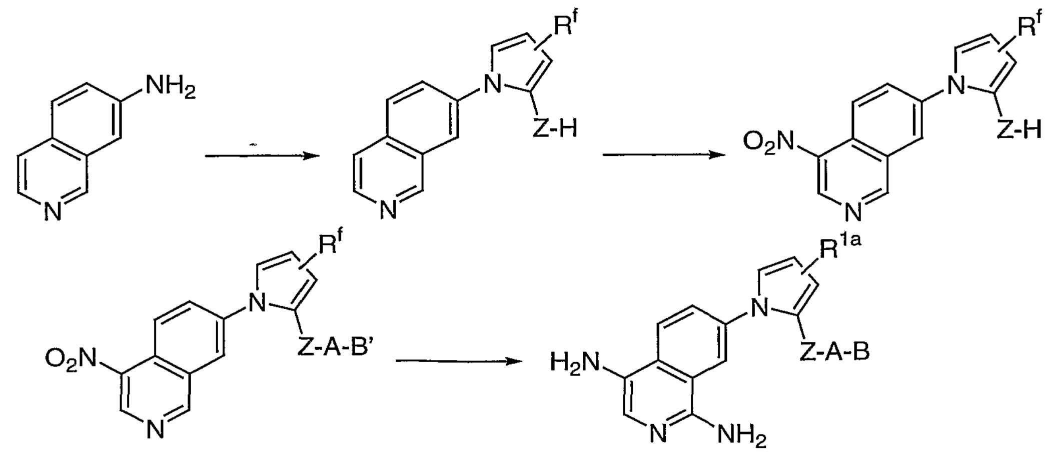
In Scheme 8a is illustrated the preparation of 5-amino substituted 1,6-naphthrydine compounds. Compounds of this type can be prepared from 3-nitro-1,6-naphthrydine (Tetrahedron **1989**, *45*, 2693). Reduction to the corresponding amine will allow for transformation to the desired 5-membered nitrogen containing heterocycle with R^f and Z-H. The 1-amino group of isoquinoline can be introduced the sequence of MCPBA oxidation to N-oxide, tosylation with tosyl chloride/pyridine and treatment with 2-aminoethanol.

Scheme 8a



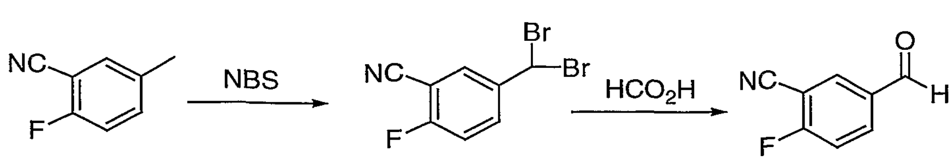
In Scheme 8b is shown how to prepare isoquinolines that contain 1,4-diamine substitution. From 7-aminoisoquinoline, the desired 5-membered nitrogen containing heterocycle with R^f and Z-H substitution may be synthesized as previously shown in Scheme 8a. Nitration to the isoquinoline 4 position may be accomplished using standard conditions to afford a 4-nitro moiety. The addition of fragment A-B′ and the 1-aminoisoquinoline portion can be accomplished as described earlier. The transformation of A-B′, R^f and the 4-nitro substituent to A-B, $R^{1a}$and a 4-amino group, respectively, is accomplished by previously outlined methods.

Scheme 8b



Scheme 9 illustrates the preparation of an intermediate for 3-aminobenzisoxazole and 3-aminoindazole. Compounds of this general type can be obtained from a fluorocyanobenzaldehyde prepared from commercially available 2-fluoro-5-methylbenzonitrile by first bis-bromination in a nonprotic solvent in the presence of AIBN or other suitable free radical initiator at a temperature ranging from ambient temperature to the reflux temperature of the selected solvent or under a UV light. The bis-bromo compound may then be converted to an aldehyde using a protic solvent in strong acidic or basic conditions at ambient temperature or higher. The aldehyde or the acid equivalent can then be converted to various C-linked ring M by methods that will be described later.

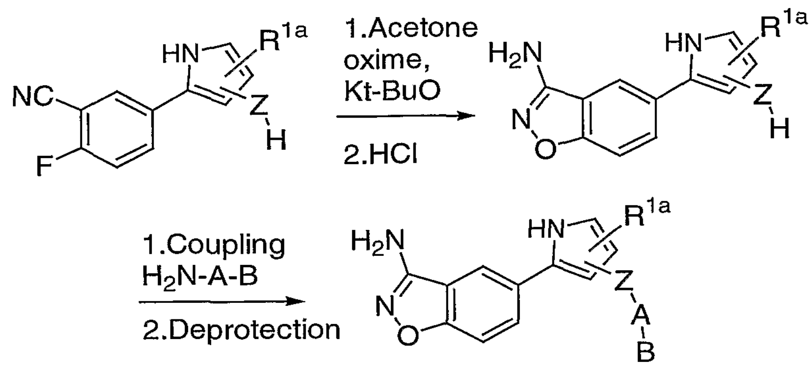
Scheme 9



Scheme 10 outlines the formation of C-linked aminobenzisoxazoles. The aminobenzisoxazole P1 can be

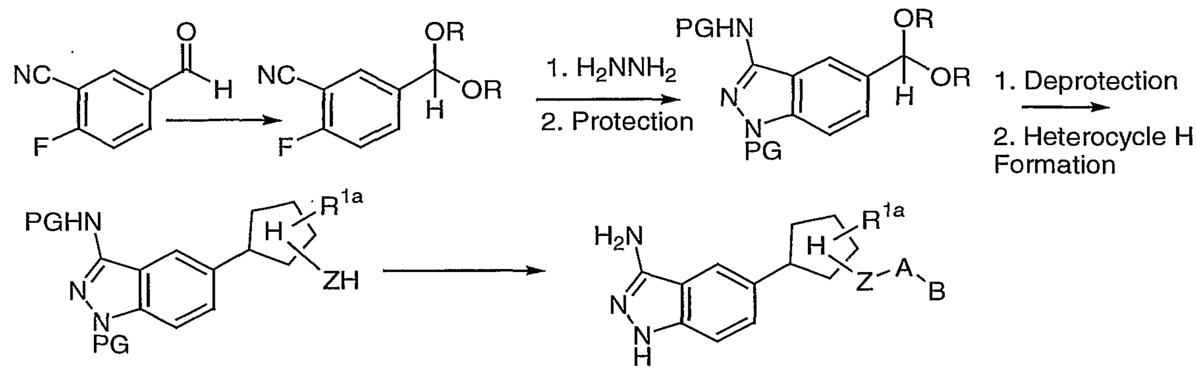
obtained by first treating the oxime of acetone with potassium t-butoxide in an aprotic polar solvent, followed by the addition of the fluorocyanophenylheterocycle H and then treatment with a protic solvent under strongly acidic conditions (*J. Heterocycl. chem.* **1989,** *26,* 1293). Coupling and deprotection as described previously gives 3-aminobenzisoxazoles of pyroles.

Scheme 10



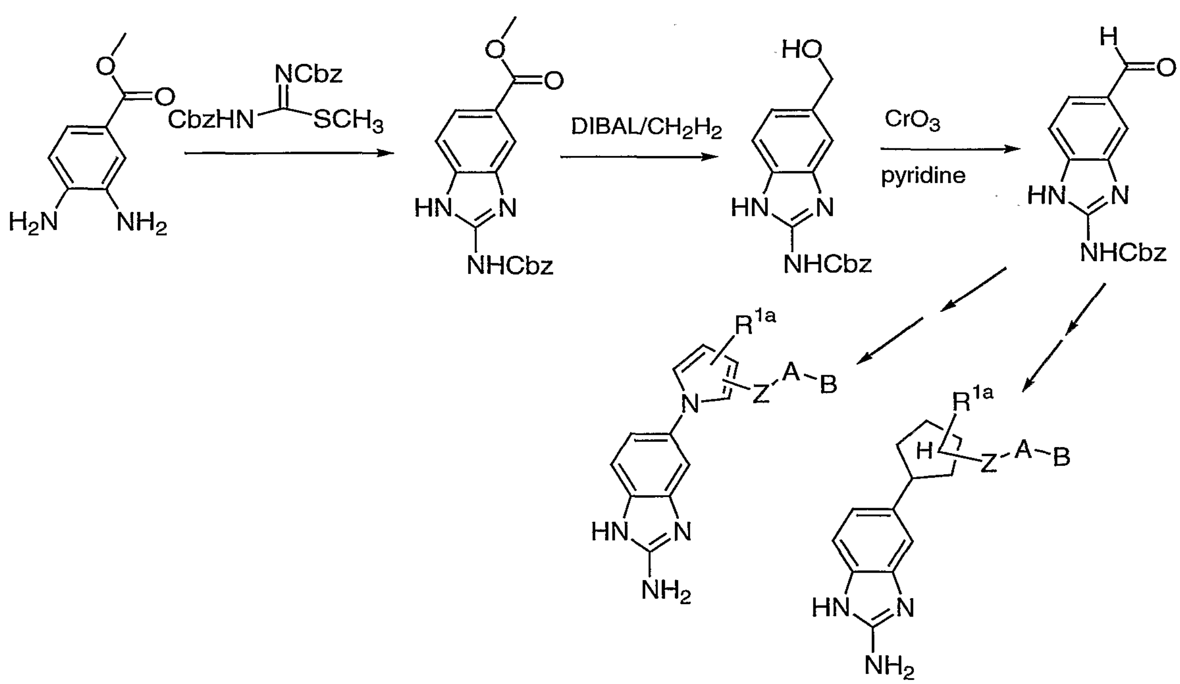
Scheme 11 outlines the formation of the C-linked 3-aminoindazoles of the present invention. Protection of the aldehyde as propylene ketal by standard conditions followed by refluxing with hydrazine in ethanol gives 3-aminoindazole ketal. Protection of the amino group with CBZCl and deprotection of the ketal with HCl/MeOH gives the aldehyde. The aldehyde or the acid equivalent can be converted to various C-linked heterocycles as described later. Coupling and deprotection as described previously gives 3-aminoindazoles of the present invention.

Scheme 11



Scheme 12 illustrates the preparation of aminobenzimidazole aldehyde that can be carried onto the C-linked or N-linked heterocycles by the methods described later in the synthesis section. Cyclization of 3,4-diaminobenzoate to give cbz- protected 2-aminobenzimidazole followed by DIBAL reduction and oxidation gives the desired aldehyde.

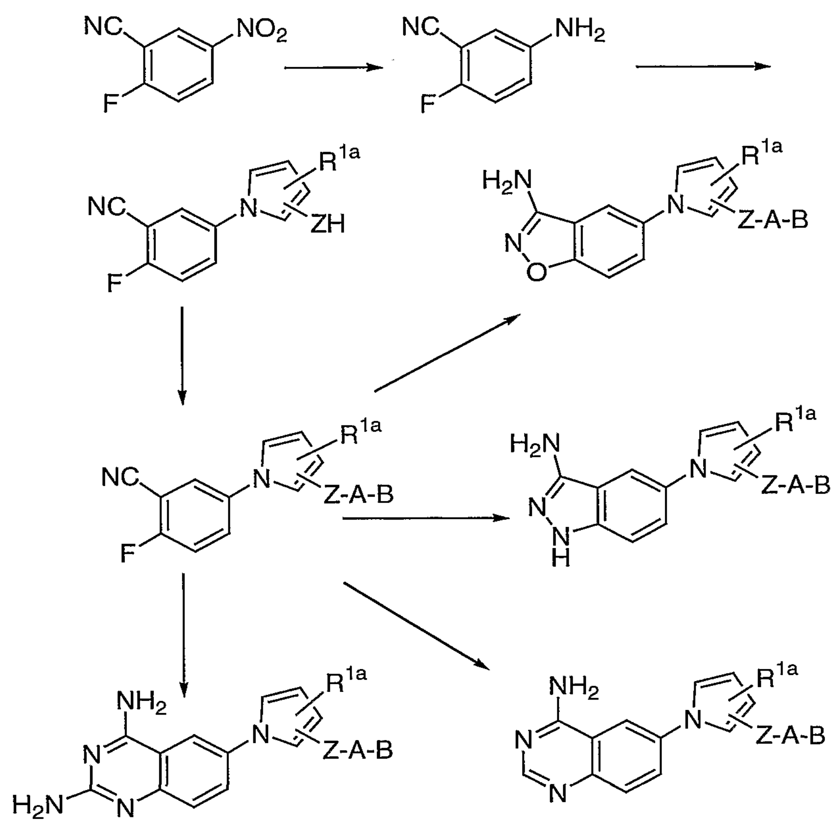
Scheme 12



Scheme 13 illustrates the preparation of N-linked aminobenzisoxazoles, aminoindazoles, diaminoquinazolines and aminoquinazolines of Formula I. Compounds of this type can be made from the aniline derivative prepared from commercially available 2-fluoro-5-nitrobenzonitrile using tin(II) chloride or other compatible reducing agents in a protic or an aprotic solvent with or without a miscible co-solvent at from ambient temperature to reflux temperature of the selected solvent

The N-linked 3-aminobenzisoxazoles and 3-aminoindazoles can be obtained as described previously. The N-linked aminoquinazoline and diaminoquinazoline P1's can be obtained by condensing the fluorocyano compound with formamidine acetate or guanidine hydrochloride (*J. Heterocycl. Chem.* **1988,** *25,* 1173).

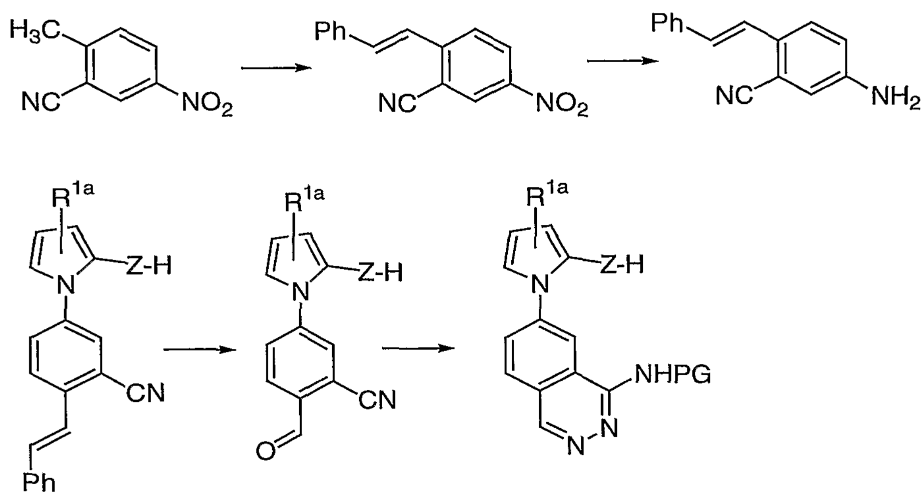
Scheme 13



Scheme 14 illustrates the preparation of 1-amino-2-benzopyrazine P1 heterocyclic intermediates leading to compounds of Formula I. Compounds of this general type can be obtained from an aminostilbene prepared from commercially available 2-cyano-4-nitrotoluene by first condensing the nitrotoluene with benzaldehyde or one of its analogs in an alcoholic solvent in the presence of an alkoxide base at a temperature ranging from -10 ^{o}C to the reflux temperature of the selected solvent. The nitrostilbene may then be reduced to aminostilbene by reaction with tin(II) chloride or another compatible reducing agent in a protic solvent with or without a miscible co-solvent at ambient temperature or higher. The aniline may then be carried on to the N-linked

or C-linked heterocycles H by the methods previously described.

Scheme 14

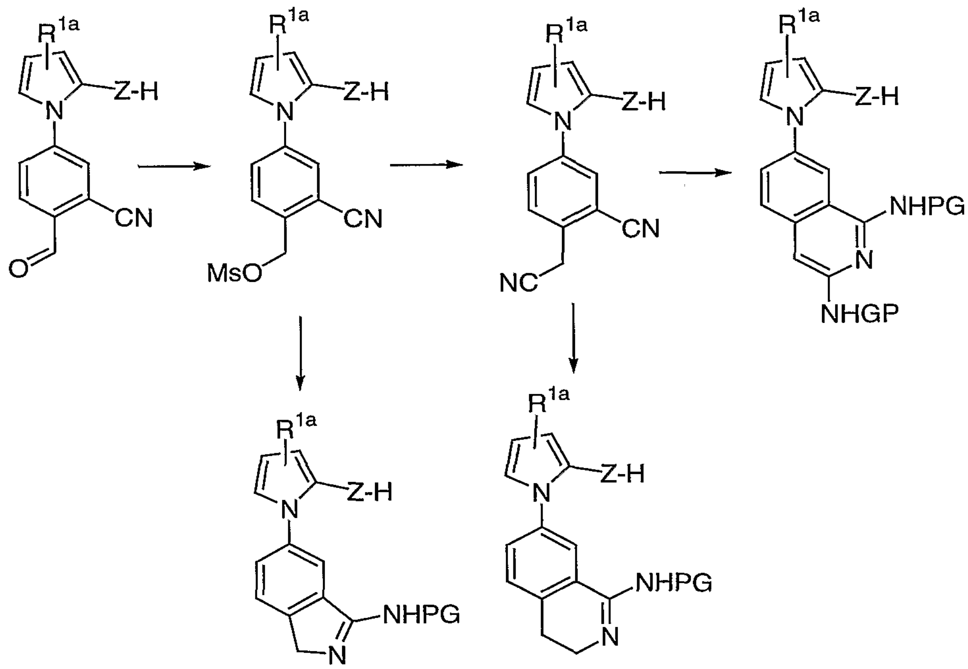


Scheme 14 also further outlines transformation of the N-linked and C-linked (not shown) heterocyclic stilbenes to give 1-aminophthalazines of Formula I. Oxidative cleavage of the stilbene double bond according to the method of Narasimhan et al (*Synth. Commun* **1985**, *15(9)*, 769) or Sheu et al (*J. Am Chem. Soc.* **1990**, *112*, 879) or their equivalent should give an aldehyde. The aldehyde can be treated with hydrazine neat or in a polar or apolar solvent at ambient temperature or up to the reflux temperature of the solvent selected to cause ring closure. Group Z-H can then be coupled with group H_2N-A-B according to the methods outlined in Scheme 2a.

The N-linked and C-linked heterocyclic 2-cyanobenzaldehydes prepared in Scheme 8 can also be used as convenient starting materials for the preparation of N-linked 1,3-diaminoisoquinoline intermediate of Scheme 9 and C-linked (not shown) 1,3-diaminoisoquinoline intermediate of Scheme 15 by appropriate adaptation of the chemistry

outlined below. The 2-cyanobenzaldehyde can be reduced to the benzylic alcohol by a hydride reducing agent, preferably sodium borohydride, then treated with a sulfonylchloride, methane sulfonyl chloride as suggested by Scheme 9 or an equivalent, using a trialkylamine base and a dry chlorocarbon solvent with cooling. The mesylate and biscyano intermediates can also be converted to the corresponding 1-aminoisoindole P1 and 1-amino-3,4-dihydroisoqunoline P1 respectively.

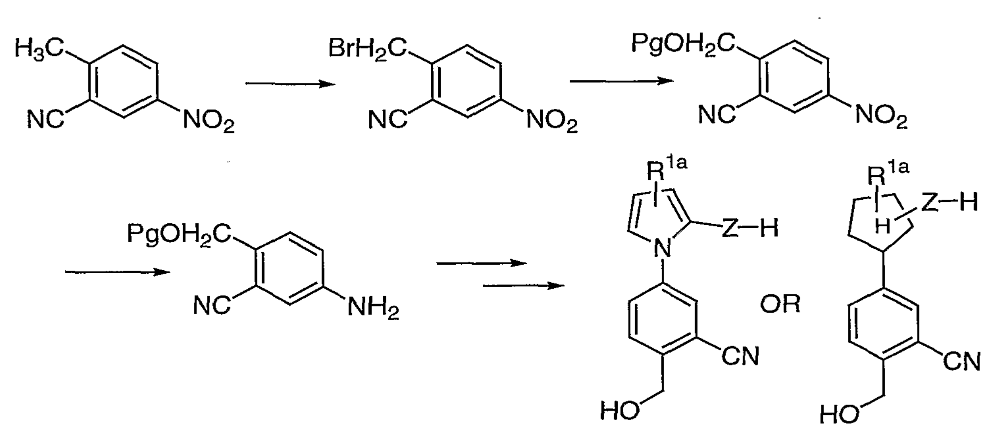
Scheme 15



Scheme 16 illustrates another approach to preparing the N-linked and C-linked heterocyclic benzylic alcohols intermediates. These compounds may be obtained from 2-cyano-4-nitro-toluene by photochemical benzylic bromination with N-bromosuccinimide in carbon tetrachloride with a sun lamp and at reflux in the presence of a catalytic amount of a radical initiator such as AIBN or dibenzoylperoxide. The benzylic bromide is then readily displaced with potassium

acetate under phase transfer conditions using 18-crown-6 as the phase transfer agent along with water and a non-miscible organic co-solvent with or without heating. The resulting acetate is then hydrolyzed with aqueous acid or by transesterification with anhydrous acid in an alcoholic solvent to give a benzylic alcohol. Depending upon the further demands of the chemistry involved in heterocycle formation step(s) the benzylic alcohol may be protected according to the methodology recommended by Greene and Wuts. The nitro group of the resulting product can then be reduced to the aniline according to the methods outlined above for Scheme 8 and then carried on to N-linked and C-linked heterocyclic benzylic alcohols of Scheme 16. It should be recognized that these benzylic alcohols can be readily transformed into the benzylic sulfonate ester intermediates of Scheme 9 or oxidized to the benzaldehyde of Scheme 8 by methods known to the skilled practitioner.

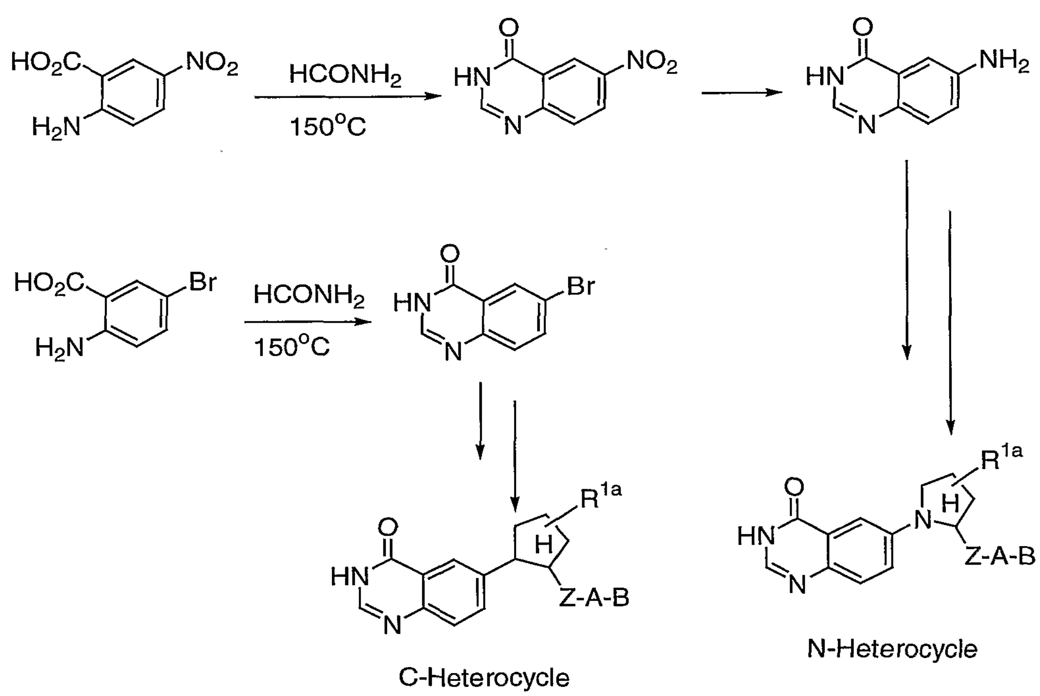
Scheme 16



The compounds of the present invention in which the D-E residue is isoquinazolin-1-one can be prepared as described in Scheme 17. For compounds that are N-linked to heterocycle M, the reaction of 5-nitroisatoic anhydride with

formamide at 150°C affords 7-nitroisoquinazolin-1-one that can be reduced to the corresponding 7-aminoisoquinazolin-1-one by a variety of reducing agents. Diazotization, reduction to the hydrazine and N-heterocycle formation can be carried out to afford the isoquinazolin-1-one N-linked to the appropriate heterocycle. For compounds that are C-linked to heterocycle M, the reaction of 5-bromoanthranilic acid with formamide at 150°C affords the 7-bromoisoquinazolin-1-one. This bromide can be converted into an aldehyde or acetyl group that can be then converted into the appropriate C-linked heterocycle.

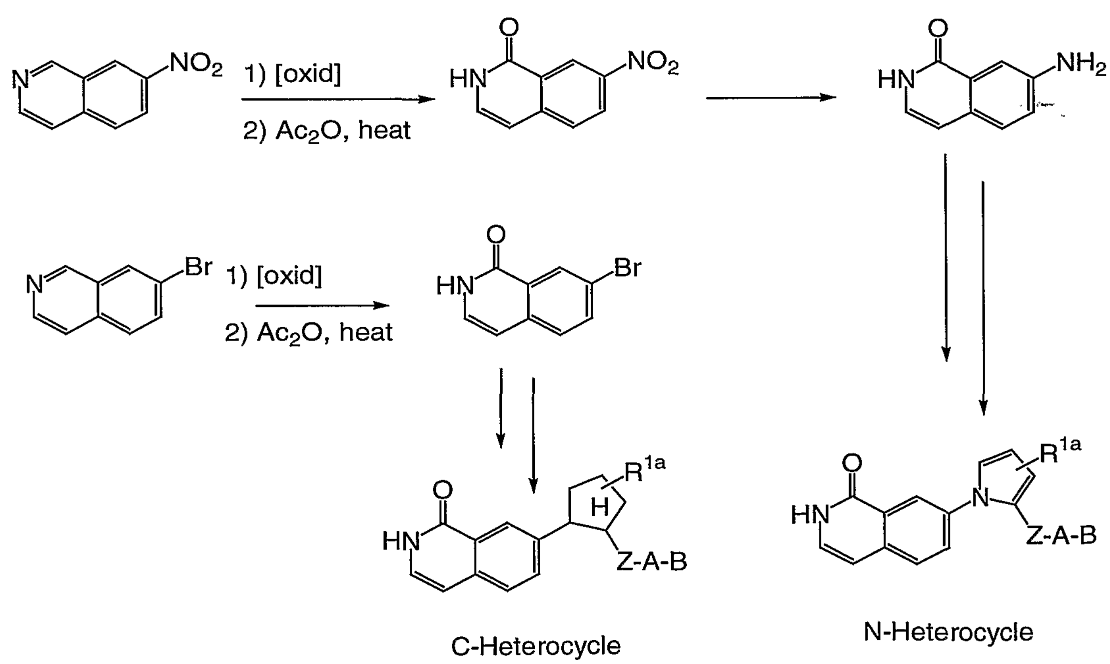
Scheme 17



The compounds of the present invention in which the D-E residue is isoquinolin-1-one can be prepared as described in Scheme 18. For compounds that are N-linked to heterocycle M, oxidation of 7-nitroisoquinoline to its corresponding N-

oxide followed by sequential treatment with acetic anhydride and then hydroxide will produce the desired 7-nitroisoquinolin-1-one. This transformation can be carried out with other reagents as well. Reduction of the nitro group and subsequent formation of the N-heterocycle will afford the isoquinolin-1-one N-linked to the appropriate heterocycle. For compounds that are C-linked to heterocycle M, analogous chemistry can be used to prepare desired 7-bromoisoquinolin-1-one, which can then be converted into the appropriate aldehyde or acetyl group for subsequent conversion to the C-linked heterocycle. One method for conversion of the bromide to an acetyl group employs palladium catalysed coupling with (ethoxyvinyl)tributyltin followed by acid hydrolysis of the intermediate vinyl ether residue.

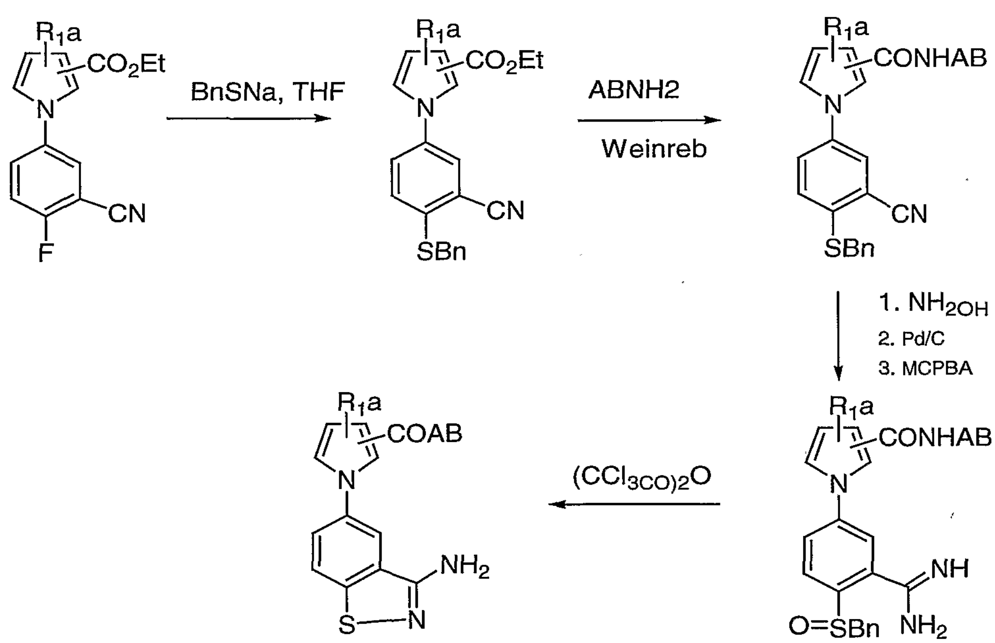
Scheme 18



Compounds wherein D-E is 3-aminobenzisothiazole are exemplified by synthesis on the pyrrole core as shown in

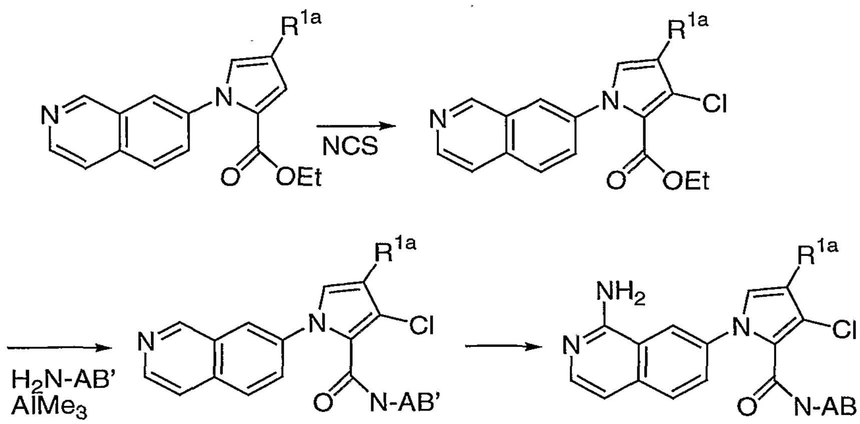
Scheme 19. The 4-fluoro-3-cyano-pyrrole intermediate as described previously can be used. Displacement of the fluoro substituent via nucleophilic aromatic substitution methodology with a thio nucleophile followed by the standard Weinreb coupling methodology should afford the desired coupled thiobenzyl intermediate. The nitrile can be converted to the amidine via standard conditions. Oxidation of the sulfide to the sulfoxide with MCPBA followed by the standard closure adopted by Wright et al for the isothiazolones with trichloroacetic anhydride should afford the desired amino-isothiazolones.

Scheme 19



Scheme 20 shows the synthesis of pyrrole ring with a chloride group. Chlorination of pyrrole starting material obtained previously in Scheme 14a with NCS forms chloropyrrole. The chloropyrrole can be reacted with an aniline in the presence of AlMe3 followed by amination as described in Scheme 14a to give the desired product.

Scheme 20



The A-B moieties can be prepared by methods known to those of skill in the art. The following publications, the contents of which are incorporated herein by reference, describe and exemplify means of preparing A-B moieties: WO97/23212, WO97/30971, WO97/38984, WO98/06694, WO98/01428, WO98/28269, WO98/28282, WO98/57937, WO98/57951, and WO99/32454.

UTILITY

The compounds of this invention are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals. The term "thromboembolic disorders" as used herein includes arterial or venous cardiovascular or cerebrovascular thromboembolic disorders, including, for example, unstable angina, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis, cerebral embolism, kidney embolisms, and pulmonary embolisms. The anticoagulant effect of compounds of the

present invention is believed to be due to inhibition of factor Xa or thrombin.

The effectiveness of compounds of the present invention as inhibitors of factor Xa was determined using purified human factor Xa and synthetic substrate. The rate of factor Xa hydrolysis of chromogenic substrate S2222 (Kabi Pharmacia, Franklin, OH) was measured both in the absence and presence of compounds of the present invention. Hydrolysis of the substrate resulted in the release of pNA that was monitored spectrophotometrically by measuring the increase in absorbance at 405 nM. A decrease in the rate of absorbance change at 405 nm in the presence of inhibitor is indicative of enzyme inhibition. The results of this assay are expressed as inhibitory constant, K_i.

Factor Xa determinations were made in 0.10 M sodium phosphate buffer, pH 7.5, containing 0.20 M NaCl, and 0.5 % PEG 8000. The Michaelis constant, K_m, for substrate hydrolysis was determined at 25°C using the method of Lineweaver and Burk. Values of K_i were determined by allowing 0.2-0.5 nM human factor Xa (Enzyme Research Laboratories, South Bend, IN) to react with the substrate (0.20 mM-1 mM) in the presence of inhibitor. Reactions were allowed to go for 30 minutes and the velocities (rate of absorbance change vs time) were measured in the time frame of 25-30 minutes. The following relationship was used to calculate K_i values:

$$(v_o-v_s)/v_s = I/(K_i\ (1 + S/K_m))$$

where:

v_o is the velocity of the control in the absence of inhibitor;

v_s is the velocity in the presence of inhibitor;

I is the concentration of inhibitor;

K_i is the dissociation constant of the enzyme:inhibitor complex;

S is the concentration of substrate;

K_m is the Michaelis constant.

Using the methodology described above, some compounds of the present invention were found to exhibit a K_i of ≤ 10 µM, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors.

Compounds tested in the above assay are considered to be active if they exhibit a K_i of ≤ 10 µM. Preferred compounds of the present invention have K_i's of ≤ 1 µM. More preferred compounds of the present invention have K_i's of ≤ 0.1 µM. Even more preferred compounds of the present invention have K_i's of ≤ 0.01 µM. Still more preferred compounds of the present invention have K_i's of ≤ 0.001 µM.

The antithrombotic effect of compounds of the present invention can be demonstrated in a rabbit arterio-venous (AV) shunt thrombosis model. In this model, rabbits weighing 2-3 kg anesthetized with a mixture of xylazine (10 mg/kg i.m.) and ketamine (50 mg/kg i.m.) are used. A saline-filled AV shunt device is connected between the femoral arterial and the femoral venous cannulae. The AV shunt device consists of a piece of 6-cm tygon tubing that contains a piece of silk thread. Blood will flow from the femoral artery via the AV-shunt into the femoral vein. The exposure of flowing blood to a silk thread will induce the formation of a significant thrombus. After forty minutes, the shunt is disconnected and the silk thread covered with thrombus is weighed. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to the opening of the AV shunt. The percentage inhibition of thrombus formation is determined for each treatment group. The ID50 values (dose that

produces 50% inhibition of thrombus formation) are estimated by linear regression.

The compounds of formula (I) may also be useful as inhibitors of serine proteases, notably human thrombin, plasma kallikrein and plasmin. Because of their inhibitory action, these compounds are indicated for use in the prevention or treatment of physiological reactions, blood coagulation and inflammation, catalyzed by the aforesaid class of enzymes. Specifically, the compounds have utility as drugs for the treatment of diseases arising from elevated thrombin activity such as myocardial infarction, and as reagents used as anticoagulants in the processing of blood to plasma for diagnostic and other commercial purposes.

Some compounds of the present invention were shown to be direct acting inhibitors of the serine protease thrombin by their ability to inhibit the cleavage of small molecule substrates by thrombin in a purified system. *In vitro* inhibition constants were determined by the method described by Kettner et al. in *J. Biol. Chem.* **265**, 18289-18297 (1990), herein incorporated by reference. In these assays, thrombin-mediated hydrolysis of the chromogenic substrate S2238 (Helena Laboratories, Beaumont, TX) was monitored spectrophotometrically. Addition of an inhibitor to the assay mixture results in decreased absorbance and is indicative of thrombin inhibition. Human thrombin (Enzyme Research Laboratories, Inc., South Bend, IN) at a concentration of 0.2 nM in 0.10 M sodium phosphate buffer, pH 7.5, 0.20 M NaCl, and 0.5% PEG 6000, was incubated with various substrate concentrations ranging from 0.20 to 0.02 mM. After 25 to 30 minutes of incubation, thrombin activity was assayed by monitoring the rate of increase in absorbance at 405 nm that arises owing to substrate hydrolysis. Inhibition constants were derived from reciprocal plots of

the reaction velocity as a function of substrate concentration using the standard method of Lineweaver and Burk. Using the methodology described above, a compound of this invention was evaluated and found to exhibit a K_i of less than 10 μm, thereby confirming the utility of the compounds of the present invention as effective thrombin inhibitors.

The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. These include other anti-coagulant or coagulation inhibitory agents, anti-platelet or platelet inhibitory agents, thrombin inhibitors, or thrombolytic or fibrinolytic agents.

The compounds are administered to a mammal in a therapeutically effective amount. By "therapeutically effective amount" it is meant an amount of a compound of the present invention that, when administered alone or in combination with an additional therapeutic agent to a mammal, is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

By "administered in combination" or "combination therapy" it is meant that the compound of the present invention and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect. Other anticoagulant agents (or coagulation inhibitory agents) that may be used in combination with the compounds of this invention include warfarin and heparin, as well as other

factor Xa inhibitors such as those described in the publications identified above under Background of the Invention.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function such as by inhibiting the aggregation, adhesion or granular secretion of platelets. Such agents include, but are not limited to, the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, and piroxicam, including pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic acid or ASA), and piroxicam are preferred. Other suitable anti-platelet agents include ticlopidine, including pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine is also a preferred compound since it is known to be gentle on the gastro-intestinal tract in use. Still other suitable platelet inhibitory agents include IIb/IIIa antagonists, thromboxane-A2-receptor antagonists and thromboxane-A2-synthetase inhibitors, as well as pharmaceutically acceptable salts or prodrugs thereof.

The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. A number of thrombin inhibitors are known to one of skill in the art and these inhibitors are contemplated to be used in combination with the present compounds. Such inhibitors include, but are not limited to, boroarginine derivatives,

boropeptides, heparins, hirudin and argatroban, including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boropeptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal a-aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin. Boropeptide thrombin inhibitors include compounds described in Kettner et al., U.S. 5,187,157 and EP 293 881 A2, the disclosures of which are hereby incorporated herein by reference. Other suitable boroarginine derivatives and boropeptide thrombin inhibitors include those disclosed in WO92/07869 and EP 471,651 A2, the disclosures of which are hereby incorporated herein by reference.

The term thrombolytics (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator, anistreplase, urokinase or streptokinase, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in EP 028,489, the disclosure of which is hereby incorporated herein by reference herein. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

Administration of the compounds of the present invention in combination with such additional therapeutic agent, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential

of side effects, thereby providing an increased margin of safety.

The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of factor Xa. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving factor Xa. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimenter that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

The compounds of the present invention may also be used in diagnostic assays involving factor Xa. For example, the presence of factor Xa in an unknown sample could be determined by addition of chromogenic substrate S2222 to a series of solutions containing test sample and optionally one of the compounds of the present invention. If production of pNA is observed in the solutions containing test sample, but not in the presence of a compound of the present invention, then one would conclude factor Xa was present.

Dosage and Formulation

The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal,

subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient,and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the thromboembolic disorder.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal

delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl callulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be

sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Representative useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil may be prepared

and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules should be washed and dried.

Tablets

Tablets may be prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection may be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution should be made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension can be prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of the present invention and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to 10 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

Where the compounds of the present invention are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of the present invention and about 50 to 150 milligrams of the anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of the present invention and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

Where the compounds of the present invention are adminstered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of the present invention, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolyic agent when administered alone may be reduced by about 70-80% when administered with a compound of the present invention.

Where two or more of the foregoing second therapeutic agents are administered with the compound of the present invention, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of the present invention and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric

coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material that affects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low-viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

Example 1

5-[(3-Amidinophenyl)aminocarbonyl]-3-[1,1']-biphenyl-5-carbomethoxymethylisoxazoline

Part A. 4-Biphenylcarboxaldehyde oxime

4-Biphenylcarboxaldehyde (2.00 g, 10.98 mmol) and hydroxylamine hydrochloride (0.95 g, 13.73 mmol) were added together with 20 mL of ethanol and 20 mL of pyridine. The mixture was stirred at room temperature under N_2 for 1 h. The solvents were removed, the residue was dissolved in EtOAc and washed with and brine. It was then dried over $MgSO_4$ and concentrated to an off-white solid (1.95 g, 90% yield). LRMS (AP^+): 198.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.19(s, 1H), 7.63 (m, 6H), 7.50-7.32 (m, 4H).

Part B. 3-([1,1']-Biphenyl-5-carbomethoxymethyl-isoxazolin-5-ylcarboxylic acid

4-Biphenylcarboxaldehyde oxime (1.95 g, 9.89 mmol) and itaconic acid monomethyl ester (1.43 g, 9.89 mmol) were dissolved in 100 mL of THF. The mixture was stirred at room temperature under N_2 and bleach (25 mL of 0.67M solution) was added dropwise. The mixture was then stirred for 3 h. The THF was removed, the residue diluted with 1N aqueous NaOH and extracted with EtOAc. The aqueous mixture was then acidified with HCl; the precipitate formed was filtered and dried to give 2.82 g of the desired product (84%). LRMS (ES^-): 338.2 $(M+H)^+$. ^1H NMR (acetone-d_6) δ 7.80(m, 6H), 7.50 (m, 2H), 7.41 (m, 1H), 4.10(m, 1H), 3.76 (m, 1H), 3.69 (s, 3H), 3.20 (m, 2H).

Part C. 3-[1,1']-Biphenyl-5-[(3-cyanophenyl)-aminocarbonyl]-5-carbomethoxymethylisoxazoline

3-[1,1']-Biphenyl-5-carbomethoxymethyl-isoxazolin-5-yl carboxylic acid (0.50 g, 1.47 mmol) was dissolved in 20 mL of CH_2Cl_2, oxalyl chloride (0.53 mL, 4.41 mmol) was added followed by a few drops of DMF. The mixture was stirred at room temperature under N_2 for 2 h. The solvent was removed, toluene was added and conc. to dryness and placed under vacuum to removed residual oxalyl chloride. The resulting solid was the dissolved in CH_2Cl_2, 3-cyanoaniline (0.26 g, 2.20 mmol) was added followed by DMAP (0.49 g, 3.67 mmol). . The mixture was stirred at room temperature under N_2 for 12 h. It was diluted with CH_2Cl_2 and washed with water, 1N HCl, and brine. The organic solution was the dried over $MgSO_4$, concentrated, and chromatographed on silica 0.18 g, 28% yield). LRMS (AP^+): 440.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.82(s, 1H), 8.10(s, 1H), 7.76-7.58(m, 7H), 7.52-7.36(m, 5H), 3.82 (q, 2H), 3.72 (s, 3H), 3.42-3.02(q, 2H).

Part D. 5-[(3-amidinophenyl)aminocarbonyl]-3-[1,1']-biphenyl-5-carbomethoxymethylisoxazoline

3-[1,1']-Biphenyl-5-[(3-cyanophenyl)-aminocarbonyl]-5-carbomethoxymethylisoxazoline (0.18 g, 0.41 mmol) was dissolved in 30 mL of $CHCl_3$ and 5 mL of MeOH. The mixture was cooled in an ice-bath and HCl gas was bubbled in until the solution was saturated (about 15 min.). The reaction mixture was sealed and stirred at room temperature for 12 h. The solvents were removed and the residue was dried under vacuum. The resulting solid was then dissolved in 20 mL of MeOH and ammonium acetate (0.19 g, 2.46 mmol) was added. The reaction mixture was sealed and stirred at room temperature for 12 h. The solvent was removed. The crude mixture was purified by HPLC (C18 reverse phase, eluted with 0.5% TFA in

CH_3CN/H_2O) to give 115 mg of the TFA salt (49%). LRMS (AP^+): 457.2 $(M+H)^+$. ^1H NMR (dmso) δ 10.30(s, 1H), 9.30(s, 2H), 9.10(s, 2H), 8.20 (s, 1H), 8.08 (d, 1H), 7.76(m, 6H), 7.60-7.38(m, 5H), 3.78 (q, 2H), 3.60 (s, 3H), 3.35-3.11(q, 2H).

Example 2

5-[(3'-Aminobenzisoxazol-5'-yl))aminocarbonyl]-3-(2'-aminosulfonyl-[1,1']-biphenyl)isoxazoline

Part A. 4-Bromobenzaldehyde oxime

4-Bromobenzaldehyde (15.0 g, 81.1 mmol) and hydroxylamine hydrochloride (7.04 g, 101.3 mmol) were added together with 50 mL of ethanol and 50 mL of pyridine. The mixture was stirred at room temperature under N_2 for 1 h. The solvents were removed, the residue was dissolved in EtOAc and washed with and brine. It was then dried over $MgSO_4$ and concentrated to an off-white solid (14.3 g, 88% yield). LRMS (ES^+): 200.0, 201.9 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.26(s, 1H), 8.10 (s, 1H), 7.49 (dd, 4H).

Part B. 4-Bromobenzaldehyde oximinoChloride

4-Bromobenzaldehyde oxime (14.3 g, 71.0 mmol) was dissolved in 200 mL of $CHCl_3$. N-Chlorosucciniamide (11.38 g, 85.2 mmol) was added. The mixture was stirred at room temperature under N_2 for 12 h. The mixture was washed with water and brine. It was then dried over $MgSO_4$ and concentrated to an off-white solid (13.5 g, 81% yield). LRMS (ES^-): 198.9, 200.9 (M-Cl). ^1H NMR ($CDCl_3$) δ 7.83 (s, 1H), 7.72 (d, 2H), 7.53 (d, 2H).

Part C. (3-Cyano-4-Fluorophenyl Acrylamide

3-Cyano-4-fluoroaniline (0.50 g, 3.67 mmol) and triethylamine (0.56 mL, 4.04 mmol) were dissolved in 50 mL

of CH_2Cl_2. Acryloyl chloride (0.35 mL, 4.04 mmol) was added. The mixture was stirred at room temperature under N_2 for 1 h. The mixture was diluted CH_2Cl_2 with and washed with water and brine. It was then dried over $MgSO_4$ and concentrated to a yellow solid (0.60 g, 86% yield. ^{1}H NMR ($CDCl_3$) δ 7.96 (m, 1H), 7.80 (m, 1H), 7.54 (bs, 1H), 7.19 (t, 1H), 6.50 (d, 1H), 6.26 (m, 1H), 5.86 (d, 1H).

Part D. 5-[(3-Cyano-4-fluoropheny)aminocarbonyl]-3-(4-bromophenyl)isoxazoline

4-Bromobenzaldehyde oximinochloride (1.11 g, 4.71 mmol) and (3-Cyano-4-Fluorophenyl Acrylamide (0.60 g, 3.14 mmol) were dissolved in 50 mL of CH_2Cl_2. A solution of triethylamine (0.66 mL, 4.71 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The mixture was stirred at room temperature under N_2 for 12 h. It was diluted CH_2Cl_2 with and washed water and brine. The mixture was filtered through P/s paper and concentrated. It was then purified by chromatography on silica gel with 30-50% EtOAc in hexane to give 0.65 g of the desired product (53%). LRMS (AP^-): 386.3, 388.2 $(M-H)^-$. ^{1}H NMR ($CDCl_3$) δ 8.62(bs, 1H), 8.14 (m, 1H), 7.72 (m, 1H), 7.56 (m, 4H), 7.19 (t, 1H), 5.29(m, 1H), 3.77 (m, 2H).

Part E. 5-[(3-Cyano-4-fluoropheny)aminocarbonyl]-3-(2'-t-Butylaminosulfonyl-[1,1']-biphenyl)isoxazoline

5-[(3-Cyano-4-fluoropheny)aminocarbonyl]-3-(4-bromophenyl)isoxazoline (0.20 g, 0.52 mmol), 2-t-butylaminosulfonylphenylboronic acid (0.20 g, 1.20 mmol), and potassium phosphate (0.44 g, 2.08 mmol) were added together with 30 mL of dioxane. The mixture was degassed and tetrakis(triphenylphosphine) palladium (0) (100 mg) was added. The mixture was degassed again and then refluxed under N_2 for 12 h. The mixture was filtered through celite

and washed with EtOAc. The filtrate was concentrated and chromatographed on silica gel with 30-50% EtOAc in hexane to give 0.11 g of the desired product (42%). LRMS (AP^+): 521.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.76(s, 1H), 8.18 (d, 1H), 8.09 (dd, 1H), 7.76 (m, 3H), 7.56 (m, 3H), 7.28 (d, 1H), 7.21 (t, 1H), 5.30(m, 1H), 3.82 (m, 2H), 3.77 (s, 1H), 1.03 (s, 9H).

Part F. 5-[(3'-aminobenzisoxazol-5'-yl))aminocarbonyl]-3-(2'-t-butylaminosulfonyl-[1,1']-biphenyl)isoxazoline

Acetohydroxamic acid (0.10 g, 1.33 mmol) was dissolved in 3 mL of DMF. Potassium carbonate (0.25 g, 1.81 mmol) was added, followed by a few drops of water. The mixture was stirred at room temperature for 30 min under N_2. A solution of 5-[(3-cyano-4-fluoropheny)aminocarbonyl]-3-(2'-t-butylaminosulfonyl-[1,1']-biphenyl)isoxazoline (0.11 g, 0.22 mmol) in 3 mL of DMF was added. The resulting mixture was stirred at room temperature for 6 days under N_2. Water was added. The precipitate formed was filtered and dried to give 90.0 mg of the desired product (77%). LRMS (AP^+): 534.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.72(s, 1H), 8.18 (m, 2H), 7.74 (d, 2H), 7.57 (m, 4H), 7.40 (s, 1H), 7.28 (d, 1H), 5.32(q, 1H), 4.46 (s, 2H), 3.82 (m, 2H), 3.72 (s, 1H), 1.05 (s, 9H).

Part G. 5-[(3'-aminobenzisoxazol-5'-yl))aminocarbonyl]-3-(2'-aminosulfonyl-[1,1']-biphenyl)isoxazoline

5-[(3'-Aminobenzisoxazol-5'-yl))aminocarbonyl]-3-(2'-t-butylaminosulfonyl-[1,1']-biphenyl)isoxazoline (90.0 mg, 0.17 mmol) was dissolved in 5 mL of TFA and heated at 80ºC for 30 min. The TFA was removed. The residue was purified by HPLC (C18 reverse phase, eluted with 0.5% TFA in CH_3CN/H_2O) to give 55 mg of the TFA salt (55%). %). LRMS (ES^+): 478.1 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.12(m, 2H), 7.79 (d, 2H), 7.70-7.50 (m, 5H), 5.36(t, 1H), 3.85 (d, 2H).

Example 3

5-Methyl-2-(2'-sulfamoyl-biphenyl-4-yl)-2H-pyrazole-3-carboxylic acid-(3-carbamimidoyl-phenyl)-amidine

Part A. Ethyl-N-(4-bromophenyl-3-methyl)pyrazole-5-carboxylate

Commercially available 4-bromophenylhydrazine (1.76g, 7.91mmol) was refluxed with 2-methhoxyimino-4-oxo-pentanoic acid ethyl ester (1.48g, 7.91mmol) in acetic acid (50 mL) overnight. The reaction mixture was cooled and concentrated in vacuo. The residue was quenched with water (100 mL) and the organics extracted with EtOAc (2x100 mL), washed with sat. sodium bicarbonate (100 mL) and dried ($MgSO_4$). Evaporation afforded tan crystals of desired product (80% yield). ESI mass spectrum z (rel. intensity) 310 (M+H, 100). ^1H NMR ($CDCl_3$) δ: 7.54 (d, J = 7.5 Hz, 2H), 7.26 (d, J = 7.0 Hz, 2H), 6.81 (s, 1H), 4.21 (q, 2H), 2.35 (s, 3H), 1.24 (t, 3H).

Part B.

3-Cyanoaniline (0.131 g, 1.11 mmol) was treated with trimethylaluminum (1.39 mL, 2.78 mmol) in dichloromethane (25 mL). After 30 min. the product from part A (0.344g, 1.11mmol) was added. The reaction mixture was stirred at room temperature for 12h, quenched with HCl (1N) and the organics separated, washed with sat. sodium bicarbonate.(100 mL) and dried ($MgSO_4$). Evaporation afford a crude product which was purified via silica gel column chromatography (hexane/ethylacetate 4:1) to afford 0.38 g of desired product. ESI mass spectrum (-ve) z (rel. intensity) 370(M-H, 100).

Part C.

The product from part B (0.38 g, 1.03 mmol) was subjected to the Suzuki reaction (sodium carbonate (2N), tol:ethanol (25 mL) and tetrakis-triphenylphosphine-palladium) with 2-tert-butylsulfonamide-phenylboronic acid (0.27 g, 1.13 mmol). The reaction mixture was refluxed for 18h cooled and quenched with water (100 mL). The organics were extracted with EtOAc (100 mL) dried and evaporated to the desired product (0.34 g, 57%). ESI mass spectrum z(rel. intensity) 536 (M+Na, 100), 514 (M+H, 100).

Part D.

The product from part D was then subjected to the Pinner amidine reaction protocol described previously to afford the title compound (0.22g); ESI mass spectrum z(rel. intensity) 474(M+H, 100). ^{1}H NMR (DMSO d_6) δ: 9.35 (b, 2H), 9.05 (bs, 2H), 8.20 (bs, 1H), 8.05 (dd, 1H), 7.89 (d, 1H), 7.57 (m, 3H) 7.46 (s, 1H), 7.35 (s, 2H), 6.93 (s, 1H), 2.34 (s, 2H).

Example 4

5-Methyl-2-(2'-sulfamoyl-biphenyl-4-yl)-2H-pyrazole-3-carboxylic acid (3-aminomethyl-phenyl)amide

The compound obtained from part D of Example 3 was subjected to a palladium (10%Pd/C) catalysed reduction in a mixture of ethanol and acetic acid (50 mL) for 18h. The mixture was filtered through a pad of Celite® washed with excess ethanol evaporated to an oil. Trifluroacetic acid (1 mL) was added and the mixture was heated at 90°C for 15 min. evaporated and purified via prep. HPLC techniques described above. ESI mass spectrum m/z (rel. int.) 462(M+H, 100); ^{1}H NMR (DMSO d_6) δ: 8.10(bs, 2H), 8.05 (dd, 1H), 7.95 (bs, 1H),

7.67 (m, 2H), 7.55 (m, 5H), 7.18 (d, 1H), 6.89 (s, 1H), 3.95 (q, 2H), 2.33 (s, 2H).

Example 5

4-[(5-chloro-2-pyridinylamino)carbonyl]-1*H*-pyrazol-5-yl 1-isopropyl-4-piperidinecarboxamide

Part A: Ethyl 5-{[(1-isopropyl-4-piperidinyl)carbonyl]amino}-1H-pyrazole-4-carboxylate.

To a mixture of ethyl 5-amino-1*H*-pyrazole-4-carboxylate (0.125 g, 0.81 mmol) in anhydrous triethylamine (15 mL) was added (1-isopropyl-4-piperidinyl)carboxylic acid chloride (0.458 g, 2.42 mmol) at rt, under nitrogen. After being stirred overnight, the reaction mixture was concentrated under reduced pressure and diluted with water. The resulted mixture was extracted with methylene chloride and the organic layers were discarded. The aqueous layer was neutralized with 1N NaOH solution and extracted with methylene chloride. The combined organic layers were dried with $MgSO_4$ and concentrated to dry to yield crude amide ester 0.088 g, which was used in next step without further purification. ESI MS: 309.4 (M^++1); APCI MS: 309.2 (M^++1).

Part B: 4-[(5-chloro-2-pyridinylamino)carbonyl]-1*H*-pyrazol-5-yl 1-isopropyl-4-piperidinecarboxamide

To a dry three-necked flask charged with trimethylaluminum (0.53 mL of 2 M solution in hexane, 0.858 mmol) was added a solution of 2-amino-5-chloropyridine (92 mg, 0.714 mmol) in anhydrous methylene chloride (5 mL) at -10°C, under nitrogen atmosphere. After stirred at -10°C for 20 min, the reaction was allowed to warm gradually to rt. To the resulted reaction mixture was added a solution of the above crude ester (~0.286 mmol) in methylene chloride (5

mL). The reaction was then heated to reflux for 24 h. The cooled mixture was quenched with 1N HCl and stirred at rt for 30 min to ensure complete hydrolysis of borane complex. The mixture was basified with aq. NaOH and extracted with methylene chloride. The combined organic layers were dried with Na_2SO_4 and concentrated to dryness. The residue was dissolved in 6 mL of MeCN/water mixture (1:1, containing 2% TFA) and applied to RP-HPLC to afford the desired compound as TFA salt (40 mg). ^{1}H NMR (CD_3OD, 300 M Hz): δ 8.27~8.17 (3H, m), 7.79 (1H, d, J = 8.7 Hz), 3.52 (3H, m), 3.34 (3H, m), 3.23 (1H, m), 3.11 (1H, m), 2.28 (1H, m), 2.02 (1H, m), 1.36 (6H, d, 6.6 Hz) ppm. ESI MS: 391 (M^++1), 389 (M^+-1); APCI MS: 391 (M^++1), 389 (M^+-1).

Example 6

1-(3-Amino-benzo[*d*]isoxazol-5-yl)-4-methyl-1*H*-pyrrole-2-carboxylic acid [4-(2-dimethylaminomethyl-imidazol-1-yl)-2-fluoro-phenyl]-amide

3-Cyano-4-fluorobenzeneboronic acid: To a solution of 5-bromo-2-fluorobenzonitrile (2.0 g, 10.0 mmol) and triisopropylborate (3.3 mL, 14.5 mmol) in THF (36 mL) at -78 °C was added dropwise, *n*-BuLi (5.6 mL, 2.5 M solution in hexanes, 1.40 mmol) over 30 min. The reaction mixture was allowed to slowly warm to room temperature and after 13 h, the reaction was a cloudy, orange solution. Aqueous HCl (14.5 mL, 2 N, 29.0 mmol) was added and the mixture was stirred for 15 min to give a yellow solution. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (1 x 50 mL), dried (Na_2SO_4), concentrated *in vacuo*, and then co-evaporated with benzene (2 x 20 mL). The residue was dried over P_2O_5 at 40 °C under vacuum for 4 h

to provide boronic acid **3** (1.55 g, 96% yield) as a white solid: ^1H NMR (300 MHz, DMSO-d_6 with 2 drops of D_2O) δ: 8.55 (s, 1H), 8.12 (t, 1H), 7.46 (t, 1H).

1-(3-Cyano-4-fluoro-phenyl)-4-methyl-1*H*-pyrrole-2-carboxylic acid methyl ester. To 4-methyl-1*H*-pyrrole-2-carboxylic acid methyl ester* (130 mg, 0.94 mmol) was added $Cu(OAc)_2$ (342 mg, 1.87 mmol), powdered 4 Å molecular sieves (350 mg), CH_2Cl_2 (3.1 mL), pyridine (0.19 mL, 2.24 mmol), and 3-Cyano-4-fluorobenzeneboronic acid (225 mg, 1.40 mmol). The reaction flask was loosely capped and stirred for 4 d at room temperature. The reaction mixture was filtered through a pad of Celite and then concentrated *in vacuo*. Chromatography of the residue on silica (gradient elution, 10-25% EtOAc/hexanes) provided 1-(3-Cyano-4-fluoro-phenyl)-4-methyl-1*H*-pyrrole-2-carboxylic acid methyl ester (155 mg, 64% yield) as a white solid: APCI-MS *m/z*: $[C_{14}H_{11}FN_2O_2 + H] = 258$; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.59-7.51 (m, 2H), 7.26 (t, 1H), 6.94 (s, 1H), 6.18 (s, 1H), 3.72 (s, 3H), 2.11 (s, 3H). *4-methyl-1*H*-pyrrole-2-carboxylic acid methyl ester was prepared in three steps following a published procedure: Lash, T. D. *et al. J. Heterocycle Chem.* **1991**, *28*, 1671.

1-(3-Cyano-4-fluoro-phenyl)-4-methyl-1*H*-pyrrole-2-carboxylic acid [4-(2-dimethylaminomethyl-imidazol-1-yl)-2-fluoro-phenyl]-amide: To 4-(2-dimethylaminomethyl-imidazol-1-yl)-2-fluoro-aniline (136 mg, 0.58 mmol) in CH_2Cl_2 (0.8 mL) was added $AlMe_3$ (1.6 mL, 2.0 M in toluene, 3.1 mmol). After 15 min, 1-(3-Cyano-4-fluoro-phenyl)-4-methyl-1*H*-pyrrole-2-carboxylic acid methyl ester (100 mg, 0.39 mmol) in CH_2Cl_2 (1 mL) was added via cannula. The reaction was heated at reflux for 3 d, cooled to room temperature and diluted with CH_2Cl_2. Aqueous HCl (3 mL, 1 M) was added, which resulted in

vigorous bubbling. Brine (2 mL) was added and the mixture was extracted with $CHCl_3$ (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Chromatography of the residue on silica (gradient elution, 5-10% methanol/ CH_2Cl_2) provided 1-(3-Cyano-4-fluoro-phenyl)-4-methyl-1*H*-pyrrole-2-carboxylic acid [4-(2-dimethylaminomethyl-imidazol-1-yl)-2-fluoro-phenyl]-amid (51 mg, 29% yield) as a yellow solid: APCI *m/z*: [$C_{25}H_{22}F_2N_6O$ + H] = 461; ^1H NMR (300 MHz, CD_3OD) δ: 7.83 (t, 1H, J = 8.45 Hz), 7.76 (dd, 1H, J = 5.50, 2.58 Hz), 7.68-7.58 (m, 2H), 7.42-7.27 (m, 3H), 7.18-7.09 (m, 2H), 6.93 (s, 1H), 3.45 (s, 2H), 2.23 (s, 3H), 2.15 (s, 6H).

1-(3-Amino-benzo[*d*]isoxazol-5-yl)-4-methyl-1*H*-pyrrole-2-carboxylic acid [4-(2-dimethylaminomethyl-imidazol-1-yl)-2-fluoro-phenyl]-amide: A round-bottomed flask was charged with acetohydroxamic acid (17 mg, 0.23 mmol), K_2CO_3 (65 mg, 0.47 mmol), and DMF (0.3 mL). The mixture was stirred for 30 min and then 1-(3-Cyano-4-fluoro-phenyl)-4-methyl-1*H*-pyrrole-2-carboxylic acid [4-(2-dimethylaminomethyl-imidazol-1-yl)-2-fluoro-phenyl]-amid (36 mg, 0.078 mmol) dissolved in DMF (2 x 0.50 mL) and water (0.05 mL) was added. The reaction mixture was stirred for 22 h at room temperature, diluted with chloroform (20 mL), and washed with water (2 x 5 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Chromatography of the residue on silica (94:5:1 $CHCl_3$/MeOH/Et_3N) provided the title compound (8.5 mg, 23% yield): APCI-MS *m/z*: [$C_{25}H_{24}FN_7O_2$ + H] = 474; ^1H NMR (300 MHz, CD_3OD) δ: 7.84 (t, 1H, J = 8.52 Hz), 7.72 (d, 1H, J = 1.71 Hz), 7.57 (dd, 1H, J = 11.37, 2.23 Hz), 7.47 (td, 1H, J = 6.9, 1.8 Hz), 7.42 (s, 1H), 7.33-7.29 (m, 2H), 7.04 (s, 1H), 6.99 (d, 1H, J = 1.5 Hz), 6.92 (s, 1H), 3.41 (s, 2H), 2.18 (s, 9H).

Example 7

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylthio-thiazole-5-yl 1-isopropyl-4-piperidinecarboxamide

The title compound was synthesized according to the procedure described in Example 5. MS(ESI): 454.0 $(M+H)^+$. 100%. HR ESIMS: calcd. for $(M^{+}+1)$: 454.1138; found: 454.1145.

Example 8

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylsulfoxide-thiazole-5-yl 1-isopropyl-4-piperidinecarboxamide

To a solution of the methylthio-thiazole compound TFA salt (46 mg, 0.081 mmol) in 5 mL of CH_2Cl_2 at $-15^{\circ}C$ was added mCPBA (14 mg, 0.081 mmol). The mixture was stirred for 1h at $-15^{\circ}C$, then allowed to warm to rt. After washing with 5% aq. $Na_2S_2O_3$, 50% aq. $NaHCO_3$, brine successively, the organic layer was dried and concentrated. The residue was applied to RP-HPLC to yield the title compound as a TFA salt (44 mg, 93%). MS(ESI): 470.0 $(M+H)^+$. 100%. HR ESIMS: calcd. for $(M^{+}+1)$: 470.1087; found: 470.1085.

Example 9

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylsulfonyl-thiazole-5-yl 1-isopropyl-4-piperidinecarboxamide

To a solution of the methylthio-thiazole compound TFA salt (61 mg, 0.11 mmol) in 5 mL of glacial acetic acid at $60^{\circ}C$ was slowly added 3 mL of an aq. solution of $KmnO_4$ (35 mg, 0.22 mmol). After addition, the reaction mixture was cooled to rt, and 0.06 mL of a saturated aq. solution of $NaHSO_3$ and 2.2 mL of an 80% aq. solution of NH_4OH were added.

The mixture was then extracted with methylene chloride. The combined organic layer was washed with aq. $NaHCO_3$, brine successively. The organic layer was dried and concentrated. The residue was applied to RP-HPLC to yield the title compound as a TFA salt (40 mg, 61%). MS(ESI): 486.0 $(M+H)^+$. 100%.

Example 10

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-n-butylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide

Part A. 5-aminothiazole-2-n-butyl-4-carboxylic acid ethyl ester

To a solution of ethyl alpha-amino-alpha-cyanoacetate (1.0 g, 7.8 mmol) and cat. amount of DMAP in 10 mL of pyridine was added veleryl chloride at 0°C. The resulted mixture was stirred overnight at rt, then quenched with methanol and evaporated to dryness under reduced pressure. The residue was diluted with 1N HCl, extracted with CH_2Cl_2, dried and concentrated to dryness under reduced pressure. The crude amide was used directly in next step.

A mixture of the crude amide and Lawesson's Reagent (3.92 g, 9.70 mmol) in 20 mL of benzene was heated to reflux overnight. The reaction mixture was quenched with aq. Na_2CO_3 after cooled to rt, extracted with ethyl acetate, and dried over Na_2CO_3. The crude product was applied to silica gel chromatography to yield the thiazole compound (712 mg, 40%).

Part B. 4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-n-butylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide

Starting from 5-aminothiazole-2-n-butyl-4-carboxylic acid ethyl ester made above, the title compound was synthesized according to the procedures described in Example

5. MS(ESI): 464.0 $(M+H)^+$. 100%. HR ESIMS: calcd. for (M^++1): 464.1887; found: 464.1885.

Example 11

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide

The title compound was synthesized according to the procedures described in Example 10. MS(ESI): 422.0 $(M+H)^+$. 100%. HR ESIMS: calcd. for (M^++1): 422.1417; found: 422.1410.

Example 12

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-phenylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide

The title compound was synthesized according to the procedures described in Example 10. MS(ESI): 484.0 $(M+H)^+$. 100%. HR ESIMS: calcd. for (M^++1): 484.1574; found: 484.1562.

Example 13

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-isopropylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide

The title compound was synthesized according to the procedures described in Example 10. MS(ESI): 450.0 $(M+H)^+$. 100%. HR ESIMS: calcd. for (M^++1): 450.1730; found: 450.1749.

Example 14

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-propylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide

The title compound was synthesized according to the procedures described in Example 10. MS(ESI): 450.0 $(M+H)^+$. 100%. HR ESIMS: calcd. for (M^++1): 450.1730; found: 450.1745.

Example 15

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-ethylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide

The title compound was synthesized according to the procedures described in Example 10. MS(ESI): 436.0 $(M+H)^+$. 100%.

Example 16

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-cyclopentylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide

The title compound was synthesized according to the procedures described in Example 10. MS(ESI): 476.0 $(M+H)^+$. 100%.

Example 17

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-cyclobutylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide

The title compound was synthesized according to the procedures described in Example 10. MS(ESI): 462.0 $(M+H)^+$. 100%.

Example 18

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-(3,4-difluorophenyl)thiazole-5-yl 1-isopropyl-4-piperidinecarboxamide

The title compound was synthesized according to the procedures described in Example 10. MS(ESI): 520.0 $(M+H)^+$. 20%.

Example 19

4-[(3-Chlorophenylamino)carbonyl]-2-methylthio thiazole-5-yl 1-isopropyl-4-piperidinecarboxamide

The title compound was synthesized according to the procedures described in Example 10. MS(ESI): 453.0 $(M+H)^+$. 100%.

Example 20

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylthio-thiazole-5-yl 4-(2'-N,N-dimethylaminomethyl phenyl)phenylcarboxamide

The title compound was synthesized according to the procedures described in Example 10. MS(ESI): 538.0 $(M+H)^+$. 50%. HR ESIMS: calcd. for $(M^{+}+1)$: 538.1138; found: 538.1168.

Example 21

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylthio-thiazole-5-yl 4-[2'-(4-hydroxypiperidylmethyl) phenyl]phenylcarboxamide

The title compound was synthesized according to the procedures described in Example 10. MS(ESI): 594.0 $(M+H)^+$. 45%.

Example 22

3-[5-(2'-Methanesulfonylbiphenyl-4-carbonyl)-3-methylpyrazol-1-ylmethyl]benzamidine

Part A. 1-(3-Cyanobenzyl)-3-methyl-1*H*-pyrazole-5-carboxylic acid ethyl ester and 1-(3-cyanobenzyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid ethyl ester.

A 100-mL round-bottom flask equipped with a stir bar was charged with 2,4-dioxopentanoic acid ethyl ester (1.58 g, 10 mmol), hydrazine hydrate (1.0 g, 20 mmol), and ethanol (20 mL). The solution was then treated with glacial acetic acid (4 mL) and heated at reflux for 4 hours. The cooled solution was poured into H_2O (50 mL) and the pH was adjusted to 10 by addition of aqueous sodium hydroxide solution. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. A mixture of 5-methyl-1*H*-pyrazole-3-carboxylic acid ethyl ester and its tautomer was recovered as a solid (1.3 g, 84%) and was carried on without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (s, 1H), 4.44 (q, 2H), 2.35 (s, 3H), 1.35 (t, 3H). A stirred solution of 5-methyl-1*H*-pyrazole-3-carboxylic acid ethyl ester and its tautomer (470 mg, 3.05 mmol) in anhydrous DMF (2 mL) was charged with anhydrous potassium carbonate (630 mg, 4.58 mmol) and α-bromo-*m*-tolunitrile (600 mg, 3.05 mmol). After 4 hours, the mixture was poured into saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Chromatography of the residue on silica provided 1-(3-cyanobenzyl)-3-methyl-1*H*-pyrazole-5-carboxylic acid ethyl ester (472 mg, 57%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6-7.3 (m, 4H), 6.6 (s, 1H), 5.7 (s, 2H), 4.3 (q, 2H), 2.3 (s, 3H), 1.3 (q, 3H); and 1-(3-cyanobenzyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid ethyl ester (346 mg, 42%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.0

(s, 1H), 7.6-7.3 (m, 4H), 6.7 (s, 1H), 5.4 (s, 2H), 4.4 (q, 2H), 2.2 (s, 3H), 1.4 (q, 3H).

3-(5-Hydroxymethylpyrazol-1-ylmethyl)benzonitrile and 3-(3-hydroxymethylpyrazol-1-ylmethyl)benzonitrile were prepared by alkyation of (2*H*-pyrazo-3-yl)methanol with α-bromo-*m*-tolunitrile. 3-(3-hydroxymethylpyrazol-1-ylmethyl)benzonitrile: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 (m, 1 H), 7.5-7.4 (m, 4 H), 6.3 (d, 1 H), 5.3 (s, 2 H), 4.7 (s, 2 H), 2.3 (s, 1 H); ESI MS *m/z* 214 $[C_{12}H_{11}N_3O + H]^+$. 3-(5-hydroxymethylpyrazol-1-ylmethyl)benzonitrile: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6-7.4 (m, 5 H), 6.3 (d, 1 H), 5.4 (s, 2 H), 4.6 (s, 2 H), 2.1 (s, 1 H); : ESI MS *m/z* 214 $[C_{12}H_{11}N_3O + H]^+$.

Part B. 3-(3-Hydroxymethyl-5-methylpyrazol-1-ylmethyl)benzonitrile.

A stirred solution of 1-(3-cyanobenzyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid ethyl ester (2.28 g, 8.5 mmol) in THF (160 mL) and H_2O (40 mL) was charged with lithium hydroxide hydrate (0.38 g, 9.1 mmol). The solution was stirred for 16 hours then heated to 40 °C for 8 hours. The cooled solution was poured into 1 N HCl (150 mL) and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to provide 1-(3-cyanobenzyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid (1.89 g, 93%): *m/z* 242 $[C_{13}H_{11}N_3O_2 + H]^+$. A portion of the crude 1-(3-cyanobenzyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid (67 mg, 0.28 mmol) was dissolved in anhydrous THF (15 mL), cooled to 0 °C then charged with triethylamine (0.07 mL, 0.5 mmol) and isobutylchloroformate (0.07 mL, 0.53 mmol). After 15 minutes, the mixture was treated with $NaBH_4$ (35 mg, 3.7 mmol) followed by ice (100 mg). The solution was warmed to room temperature then

poured into 2 N HCl and extracted with ethyl acetate. The combined organic extracts were washed with $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Chromatography of the residue on silica provided 3-(3-hydroxymethyl-5-methylpyrazol-1-ylmethyl)benzonitrile (43 mg, 67%): ESI MS *m/z* 228 $[C_{13}H_{13}N_3O + H]^+$. Structure was confirmed by NOE difference spectroscopy.

Part C. 3-[5-(4-Chlorobenzoyl)-3-methylpyrazol-1-ylmethyl]benzonitrile.

A stirred solution of 1-(3-cyanobenzyl)-3-methyl-1*H*-pyrazole-5-carboxylic acid ethyl ester (12.8 g, 47.6 mmol) in THF (40 mL) and H_2O (10 mL) was charged with lithium hydroxide hydrate (2.2 g, 52.3 mmol). The solution was stirred for 16 hours, poured into 1 N HCl and extracted with ethyl acetate. The organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to provide 1-(3-cyanobenzyl)-3-methyl-1*H*-pyrazole-5-carboxylic acid (9.7 g, 84%). A solution of 2-(3-cyano-benzyl)-5-methyl-2*H*-pyrazole-3-carboxylic acid (1.0 g, 4.2 mmol) in THF (10 mL) was treated with *N,N*-carbonyl diimidazole (972 mg, 6.0 mmol) and stirred for 1 hour, then methoxylamine hydrochloride (485 mg, 5.0 mmol) was added. After 2 hours, the reaction mixture was concentrated. The residue was dissolved in THF (10 mL), cooled to 0 ºC and treated with 1 M 4-chlorophenyl magnesium bromide (10 mL, 10 mmol), stirred for 10 minutes and quenched with saturated aqueous NH_4Cl. The mixture was diluted with water and extracted with CH_2Cl_2. The organic extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica to provide 3-[5-(4-chlorobenzoyl)-3-methylpyrazol-1-ylmethyl]benzonitrile (575 mg, 41%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.8-7.35 (m, 8H), 6.5 (s, 1H), 5.7 (s, 2H), 2.4 (s, 3H).

Part D. 3-[3-Methyl-5-(2′-methylsulfanylbiphenyl-4-carbonyl)pyrazol-1-ylmethyl]benzonitrile.

A mixture of 3-[5-(4-chlorobenzoyl)-3-methylpyrazol-1-ylmethyl]benzonitrile (550 mg, 1.64 mmol), 2-thiomethylphenyl boronic acid (500 mg, 3.2 mmol), potassium fluoride (967 mg, 16.4 mmol), and dimethoxyethane was purged with a stream of nitrogen for 15 minutes. The solution was treated with tris(dibenzylideneacetone)-dipalladium(0) (140 mg, 0.12 mmol) and biphenyl-2-yl-di-*tert*-butyl phosphane (115 mg, 0.39 mmol). The flask was equipped with a condenser and heated to 80 °C for 2 days. The cooled solution was diluted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography on silica to provide 3-[3-methyl-5-(2′-methylsulfanylbiphenyl-4-cabonyl)-pyrazol-1-ylmethyl]benzonitrile (703 mg, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.9-7.15 (m, 12H), 6.6 (s, 1H), 5.75 (s, 2H), 2.42 (s, 3H), 2.38 (s, 3H).

Part E. 3-[5-(2′-Methanesulfonylbiphenyl-4-cabonyl)-3-methylpyrazol-1-ylmethyl]benzonitrile.

A stirred solution of 3-[3-methyl-5-(2′-methylsulfanylbiphenyl-4-carbonyl)pyrazol-1-ylmethyl]benzonitrile (680mg, 1.42 mmol) and potassium carbonate (2.0 g, 14.4 mmol) in CH_2Cl_2 (10 mL) was treated with *m*-CPBA (481 mg, 2.8 mmol). The mixture was stirred at room temperature for 12 hours, diluted with ethyl acetate. The organic layer was washed with saturated $Na_2S_2O_3$, saturated $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography over silica to afford 3-[5-(2′-methanesulfonylbiphenyl-4-carbonyl)-3-methylpyrazol-1-ylmethyl]benzonitrile (557 mg,

86%): ^1H NMR (300 MHz, $CDCl_3$) δ 8.25-7.35 (m, 12H), 6.6 (s, 1H), 5.8 (s, 2H), 2.75 (s, 3H), 2.38 (s, 3H).

Part F. 3-[5-(2′-Methanesulfonylbiphenyl-4-carbonyl)-3-methylpyrazol-1-ylmethyl]benzamidine.

Anhydrous HCl gas was bubbled through a solution of 3-[5-(2′-methylsulfanylbiphenyl-4-carbonyl)-3-methylpyrazol-1-ylmethyl]benzonitrile (250 mg, 0.56 mmol) in ethanol (5.0 mL) for 30 minutes. The reaction vessel was sealed and maintained at –20 °C. The reaction was monitored by HPLC and additional hydrochloric acid gas was introduced after 24 hours. The reaction was concentrated and the residue was dissolved in anhydrous ethanol (10 mL). An excess of ammonium carbonate was added and stirring was continued at room temperature for 24 hours. The reaction was concentrated and the residue was purified by semi-preparative HPLC to afford 3-[5-(2′-methanesulfonylbiphenyl-4-carbonyl)-3-methylpyrazol-1-ylmethyl]benzamidine-*N*-trifluoroacetate (180 mg, 55%): ESI MS *m/z* 473 $[C_{26}H_{24}N_4O_3S + H]^+$.

Example 23

6-Methoxynaphthalene-2-carboxylic acid [1-(3-carbamimidoylbenzyl)-5-methyl-1*H*-pyrazol-3-ylmethyl]amide

Part A. 3-(3-Hydroxymethyl-5-methylpyrazol-1-ylmethyl)benzonitrile.

A 500-mL round-bottom flask equipped with a stir bar was charged with 1-(3-cyanobenzyl)-3-methyl-1*H*-pyrazole-5-carboxylic acid ethyl ester (3.53 g, 13.1 mmol), THF (200 mL), H_2O (50 mL), and LiOH (670 mg, 16 mmol). After 24 h, the reaction was acidified with 1 M HCl (90 mL) and extracted with EtOAc. The combined organic extracts were

dried ($MgSO_4$) and evaporated in vacuo. The residue was dissolved in THF (60 mL) then Et_3N (3.3 mL, 23.8 mmol) was added. The reaction was cooled to 0 °C and isobutyl chloroformate (3.1 mL, 23.9 mmol) was added under N_2. After 5 h, $NaBH_4$ (1.48 g, 39.2 mmol) was added and the reaction was stirred for an additional 1 h then quenched with crushed ice. Water (100 mL) and EtOAc (50 mL) were added and the reaction was acidified to ~pH 1 (2 M HCl). The layers were separated and the acidic aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo. Chromatography of the residue on silica (98:2 CH_2Cl_2/MeOH) provided 3-(3-hydroxymethyl-5-methylpyrazol-1-ylmethyl)benzonitrile as a white solid (894 mg, 41%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, 1H), 7.44 (dd, 1H), 7.33-7.31 (m, 2H), 6.10 (s, 1H), 5.27 (s, 2H), 4.65 (s, 1H), 2.20 (s, 3H); ESI MS *m/z* 228 [$C_{13}H_{13}N_3O + H]^+$.

Part B. 3-(3-Azidomethyl-5-methylpyrazol-1-ylmethyl)benzonitrile.

A 100-mL round-bottom flask equipped with a stir bar was charged with 3-(3-hydroxymethyl-5-methylpyrazol-1-ylmethyl)benzonitrile (894 mg, 3.94 mmol), CH_2Cl_2 (30 mL), and Hunig's base (1.1 mL, 6.3 mmol), then methanesulfonyl chloride (0.95 mL, 12.3 mmol) was added. After 72 h, the reaction was evaporated in vacuo. The residue was dissolved in DMF (40 mL) then sodium azide (803 mg, 12.4 mmol) was added. After 24 h, H_2O (200 mL) was added into the reaction mixture and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. Chromatography of the residue on silica (1:2 EtOAc/hexanes) provided 3-(3-azidomethyl-5-methylpyrazol-1-ylmethyl)benzonitrile as a light yellow oil (846 mg, 85%): ^1H

NMR (300 MHz, $CDCl_3$) δ 7.57 (d, 1H), 7.44 (dd, 1H), 7.33-7.28 (m, 2H), 6.13 (s, 1H), 5.29 (s, 2H), 4.30 (s, 2H), 2.22 (s, 3H); ESI MS *m/z* 253 $[C_{13}H_{12}N_6 + H]^+$.

Part C. 3-(3-Aminomethyl-5-methylpyrazol-1-ylmethyl)benzonitrile.

A 100-mL round-bottom flask equipped with a stir bar was charged with 3-(3-azidomethyl-5-methylpyrazol-1-ylmethyl)benzonitrile (846 mg, 3.36 mmol), triphenylphosphine (982 mg, 3.74 mmol), and THF (40 mL). After 24 hours, H_2O (30 mL) was added and stirring was continued for another 24 h then the organic solvent was evaporated off. The aqueous solution was acidified (~ pH 1, 2 M HCl) and extracted with EtOAc (3 x 30 mL). The aqueous layer was basified (~ pH 10, 1 M NaOH) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. Chromatography of the residue on silica (9:1 CH_2Cl_2/MeOH) provided 3-(3-aminomethyl-5-methylpyrazol-1-ylmethyl)benzonitrile as a white solid (599 mg, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, 1H), 7.43 (dd, 1H), 7.33-7.30 (m, 2H), 6.03 (s, 1H), 5.26 (s, 2H), 3.840 (s, 2H), 2.18 (s, 3H); ESI MS *m/z* 227 $[C_{13}H_{14}N_4 + H]^+$.

Part D. 6-Methoxynaphthalene-2-carboxylic acid [1-(3-cyanobenzyl)-5-methyl-1*H*-pyrazol-3-ylmethyl]amide.

3-(3-Aminomethyl-5-methylpyrazol-1-ylmethyl)benzonitrile (204 mg, 0.903 mmol) in CH_2Cl_2 (10 mL) was added via cannula to a stirred solution of 6-methoxy-2-naphthoyl chloride (433 mg, 1.96 mmol), DMAP (363 mg, 2.97 mmol), pyridine (0.8 mL, 9.9 mmol), and CH_2Cl_2 (20 mL) at 0 °C under N_2. After 3 h at room temperature, the reaction was added to saturated $NaHCO_3$ solution (200 mL) and extracted

with CH_2Cl_2 (3 x 30 mL). The combined organics were dried over $MgSO_4$ and reduced in vacuo. Chromatography of the residue on silica (95:5 CH_2Cl_2/MeOH) provided 6-methoxynaphthalene-2-carboxylic acid [1-(3-cyanobenzyl)-5-methyl-1*H*-pyrazol-3-ylmethyl]amide as a white solid (293 mg, 79%): ESI MS *m/z* 411 $[C_{25}H_{22}N_4O_2 + H]^+$.

Part E. 6-Methoxynaphthalene-2-carboxylic acid [1-(3-carbamimidoylbenzyl)-5-methyl-1*H*-pyrazol-3-ylmethyl]amide

The title compound was prepared by Pinner reaction: ESI MS *m/z* 428 $[C_{25}H_{25}N_5O_2 + H]^+$.

Example 24

3-{5-Methyl-3-[(naphthalene-2-sulfonylamino)methyl]pyrazol-1-ylmethyl}benzamidine

The title compound was prepared similarly from naphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-5-methyl-1*H*-pyrazol-3-ylmethyl]amide: ESI MS *m/z* 434 $[C_{23}H_{23}N_5O_2S + H]^+$.

Example 25

3-{3-[(6-Methoxynaphthalene-2-sulfonylamino)methyl-5-methylpyrazol-1-ylmethyl}benzamidine

The title compound was prepared similarly from 6-methoxylnaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-5-methyl-1*H*-pyrazol-3-ylmethyl]amide: ESI MS *m/z* 464 $[C_{24}H_{25}N_5O_3S + H]^+$.

Example 26

3-{3-[(7-Chloronaphthalene-2-sulfonylamino)methyl]pyrazol-1-ylmethyl}benzamidine

Part A. 2-(4-Methoxybenzyl)-2*H*-pyrazol-3-yl]methanol.

A 500-mL round-bottom flask equipped with a stir bar was charged with 2-(4-methoxybenzyl)-2*H*-pyrazole-3-carbaldehyde (5.89 g, 27.3 mmol) and THF (140 mL) then cooled to 0 °C under N_2. DIBAL-H (30 mL, 30 mmol, 1 M in hexanes) was added to the solution over 10 min. After 30 min, the reaction was quenched with ice H_2O (100 mL) and acidified with 2 M HCl (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. Recrystallization from hexanes/CH_2Cl_2 provided 2-(4-methoxybenzyl)-2*H*-pyrazol-3-yl]methanol as a white solid (4.64 g, 78%): ESI MS *m/z* 219 $[C_{12}H_{14}N_2O_2 + H]^+$.

Part B. (2*H*-Pyrazol-3-yl)methanol.

A 500-mL round-bottom flask equipped with a stir bar was charged with 2-(4-methoxybenzyl)-2*H*-pyrazol-3-yl]methanol (4.79 g, 22.0 mmol) and CH_3CN (100 mL). Ceric ammonium nitrate (27.26 g, 49.7 mmol) in H_2O (100 mL) was added to the solution. After 4 h, $Na_2S_2O_3$ (3.5 g) was added then was adsorbed onto silica gel. Chromatography of the pre-adsorbed residue on silica (gradient, 90:10 to 85:15 CH_2Cl_2/MeOH) provided (2*H*-pyrazol-3-yl)methanol as an amber oil (1.62 g, 75%): ESI MS *m/z* 99 $[C_4H_6N_2O + H]^+$.

The alcohol was similarly converted to amine as described above and coupled with the corresponding sulfonic acid.

Part C. 3-{3-[(7-Chloronaphthalene-2-sulfonylamino)methyl]pyrazol-1-ylmethyl}benzamidine

The title compound was prepared similarly from 7-chloronaphthalene-2-sulfonic acid[1-(3-cyanobenzyl)-1*H*-pyrazol-3-ylmethyl]amide: ESI MS *m/z* 454 $[C_{22}H_{20}ClN_5O_2S + H]^+$.

Example 27

3-{3-[(7-Methoxynaphthalene-2-sulfonylamino)methyl]pyrazol-1-ylmethyl}benzamidine

The title compound was prepared similarly from 7-methoxynaphthalene-2-sulfonic acid [1-(3-cyanobenzyl)-*1H*-pyrazol-3-ylmethyl]amide: ESI MS *m/z* 450 $[C_{23}H_{20}N_4O_2S + H]^+$.

Example 28

1-Isopropylpiperidine-4-carboxylic acid [4-(4-chlorobenzoylamino)furazan-3-yl]amide

Part A. *N*-(4-Aminofurazan-3-yl)-4-chlorobenzamide.

A 25-mL round-bottom flask equipped with a stir bar was charged with diaminofurazan (100 mg, 1.0 mmol), pyridine (5.0 mL), and 4-chlorobenzoyl chloride (128 μL, 1.00 mmol). The reaction mixture was stirred under N_2 at 25 °C for 18 hours then was concentrated in vacuo. The residual pyridine was removed by azeotropic distillation with 4:1 chloroform/ethanol. Chromatography of the residue on silica provided *N*-(4-aminofurazan-3-yl)-4-chlorobenzamide as a white solid (108 mg, 45%): ^1H NMR (300 MHz, $CDCl_3$) δ 11.26 (br s, 1H), 8.04 (d, 2H), 7.47 (d, 2H), 5.32 (br s, 2H); ESI MS (negative mode) *m/z* 237 $[C_9H_7ClN_4O_2 - H]^-$.

Part B. 1-Isopropylpiperidine-4-carboxylic acid [4-(4-chlorobenzoylamino)furazan-3-yl]amide.

A 100-mL round-bottom flask equipped with a stir bar was charged with 1-isopropylpiperidine-4-carboxylic acid (520 mg, 2.0 mmol) in CH_2Cl_2, (24.0 mL, 0.15 M) then cooled to 0 °C under N_2. Oxalyl chloride (2.1 mL, 12.0 mmol) was added dropwise followed by DMF (50 μL) and the mixture was

warmed to room temperature. After 18 hours, the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (24.0 mL, 0.15 M), cooled to 0 °C, and treated with pyridine (320 uL, 4.0 mmol) and *N*-(4-aminofurazan-3-yl)-4-chlorobenzamide (200 mg, 0.84 mmol) in one portion. The mixture was warmed to room temperature and stirred for 18 hours. The reaction mixture was washed with $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL) then dried over anhydrous Na_2SO_4. The residue was purified by column chromatography on silica to provide 1-isopropylpiperidine-4-carboxylic acid [4-(4-chlorobenzoylamino)-furazan-3-yl]amide as a white solid (192 mg, 58%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, 2H), 7.50 (d, 2H), 5.5 (m, 1H), 3.00-2.92 (m, 2H), 2.88-2.72 (m, 1H), 2.58-2.48 (m, 1H), 2.29-2.15 (m, 2H), 2.04-1.91 (m, 4H), 1.74-1.69 (m, 1H), 1.07-1.03 (m, 6 H); ESI MS *m/z* 392 $[C_{18}H_{22}ClN_5O_3 + H]^+$.

Example 29

1-Isopropylpiperidine-4-carboxylic acid [5-(4-chlorobenzoylamino)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]amide

Part A. *N*-(6-Amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4-chlorobenzamide

The title compound was prepared similarly from 5,6-diamino-1,3-dimethyluracil as a white solid (390 mg, 86%): ^1H NMR (300 MHz, DMSO-d_6) δ 9.00 (s, 1H), 7.99 (d, 2H), 7.55 (d, 2H), 6.76 (br s, 2H), 3.33 (s, 3H), 3.13 (s, 3H); ESI MS *m/z* 309 $[C_{13}H_{13}ClN_4O_3 + H]^+$.

Part B. 1-Isopropylpiperidine-4-carboxylic acid [5-(4-chlorobenzoylamino)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]amide

The title compound was prepared similarly as a yellow solid from *N*-(6-Amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4-chlororobenzamide: ESI-MS *m/z* 462 $[C_{22}H_{28}ClN_5O_4 + H]^+$.

Example 30

1-Isopropylpiperidine-4-carboxylic Acid [4-(5-Chloropyridin-2-ylcarbamoyl)-2-methyl-2*H*-pyrazol-3-yl]amide

Trimethylaluminum (0.39 mL, 0.78 mmol) was added dropwise to a solution of 2-amino-4-chloropyridine (120 mg, 0.93 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After 30 minutes, the reaction was warmed to room temperature and stirred for an additional 30 minutes. The resulting mixture was added to a solution of 5-[(1-isopropylpiperidine-4-carbonyl)amino]-1-methyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (99 mg, 0.31 mmol) in CH_2Cl_2 (5 mL) and heated to reflux. After 16 hours, the reaction was cooled and quenched with 1 N HCl. After stirring for 30 minutes, the solution was made basic with 2 N NaOH (pH 10) and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography to afford 1-isopropylpiperidine-4-carboxylic acid [4-(5-chloropyridin-2-ylcarbamoyl)-2-methyl-2*H*-pyrazol-3-yl]amide (33 mg, 27%): ESI MS *m/z* 405 $[C_{19}H_{25}ClN_6O_2 + H]^+$.

Example 31 AG2418-00

1-Isopropylpiperidine-4-carboxylic Acid [4-(5-Chloropyridin-2-ylcarbamoyl)-2-phenyl-2*H*-pyrazol-3-yl]amide

The title compound was prepared in a similar manner from 5-[(1-isopropylpiperidine-4-carbonyl)amino]-1-phenyl-

1*H*-pyrazole-4-carboxylic acid ethyl ester: ESI MS *m/z* 467 $[C_{24}H_{27}ClN_6O_2 + H]^+$.

Example 32

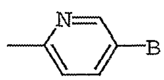
1-Isopropylpiperidine-4-carboxylic Acid [4-(5-Chloropyridin-2-ylcarbamoyl)-3-methylisothiazol-5-yl]amide

The title compound was prepared in a similar manner from 5-[(1-isopropylpiperidine-4-carbonyl)amino]-3-methylisothiazole-4-carboxylic acid ethyl ester: ESI MS *m/z* 422 $[C_{19}H_{24}ClN_5O_2S+ H]^+$.

The following table contains representative examples of the present invention. Each entry in the table is to be paired with each formula at the start of the table. For example, example 1 is to be paired with each of the formulae and each of these pairs is to be paired with each of the listed A and B groups.

The following nomenclature is intended for group A in the following tables.


phenyl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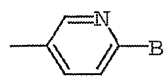
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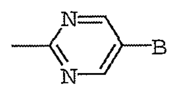
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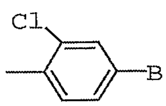
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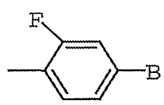
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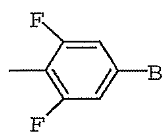
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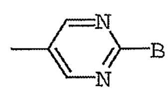
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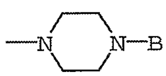
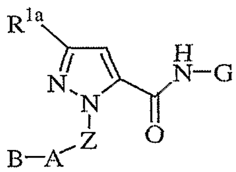

piperidinyl

Table 1



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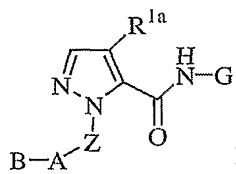

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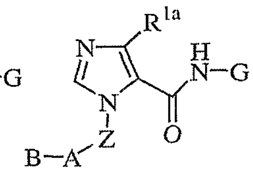

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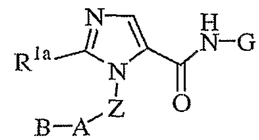

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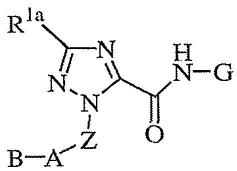

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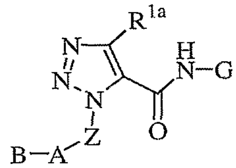

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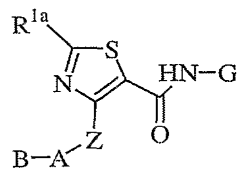

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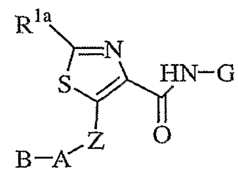

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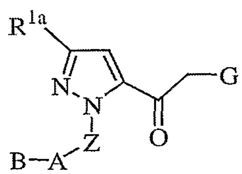

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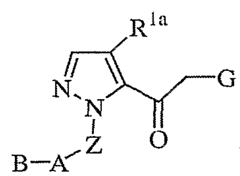

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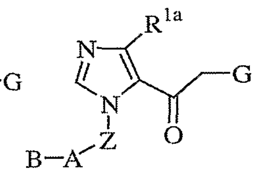

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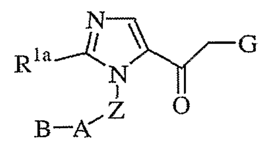

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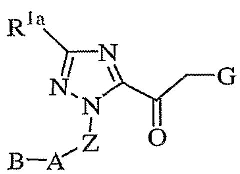

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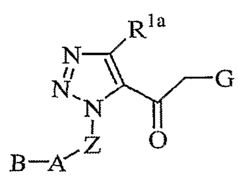

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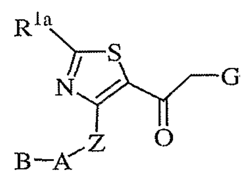

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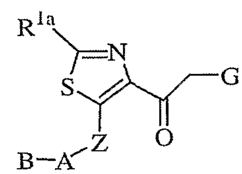

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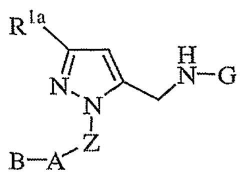
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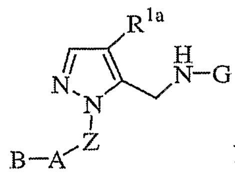
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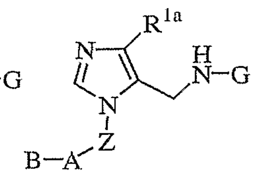
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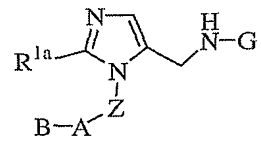
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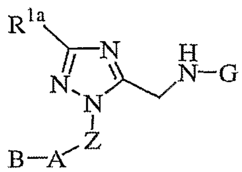
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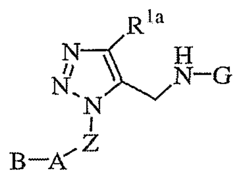
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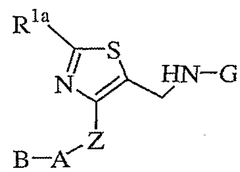
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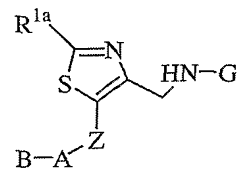
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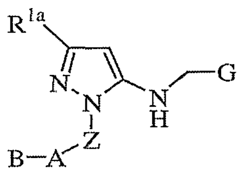
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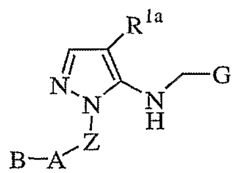
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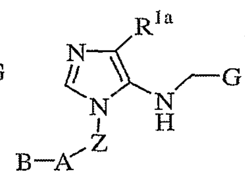
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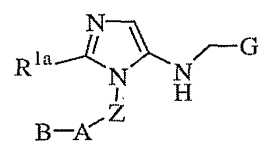
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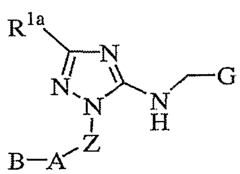
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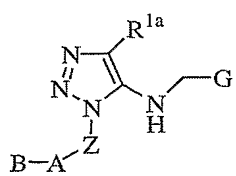
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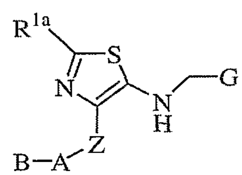
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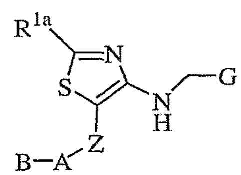
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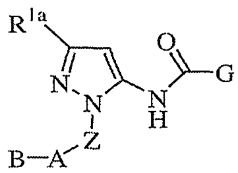
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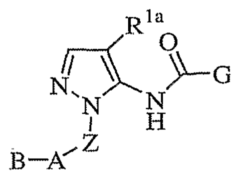
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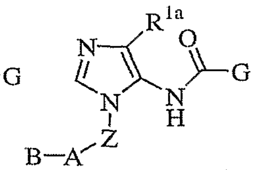
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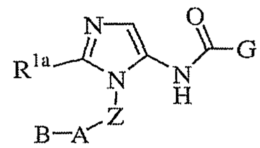
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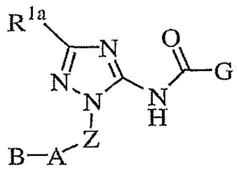
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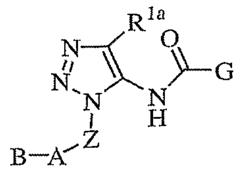
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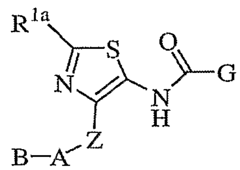
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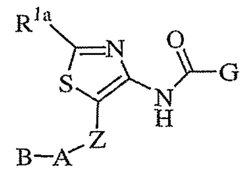
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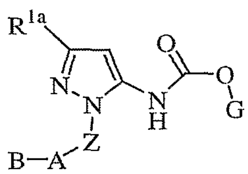
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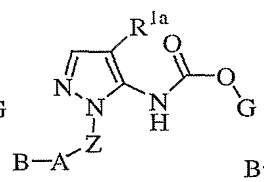
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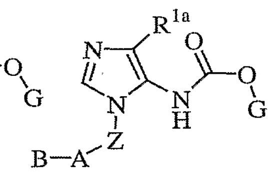
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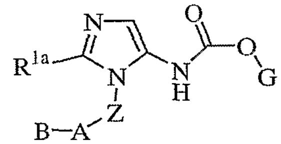
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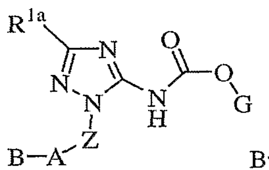
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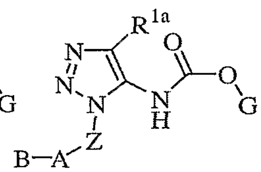
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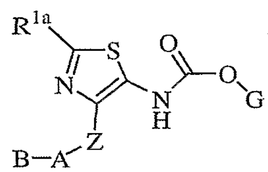
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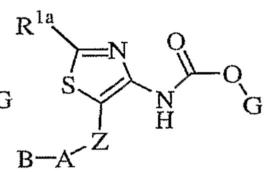
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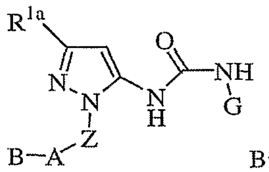

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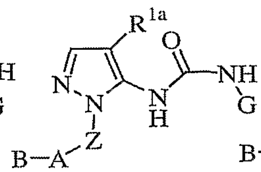

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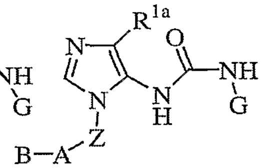

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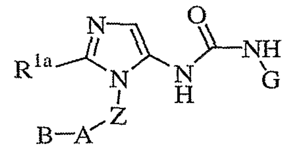

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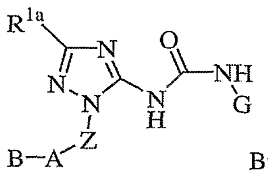

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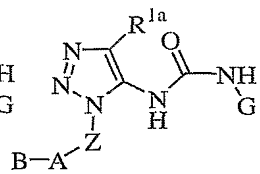

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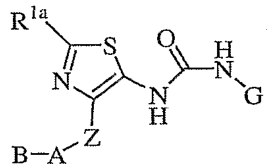

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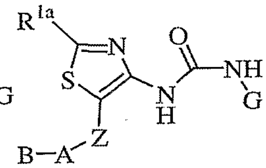

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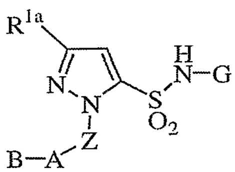

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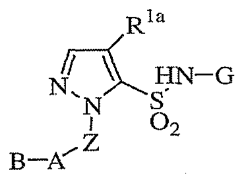

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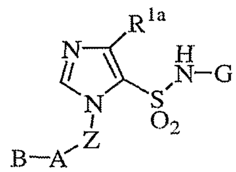

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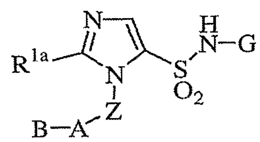

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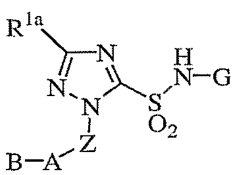

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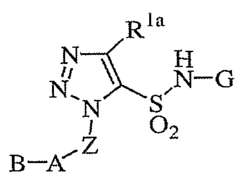

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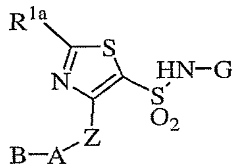

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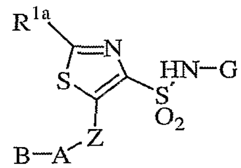

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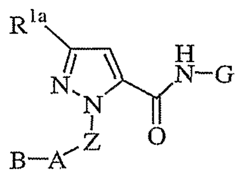

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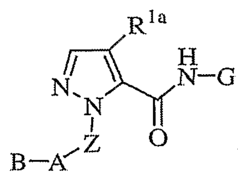

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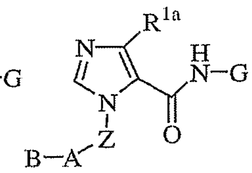

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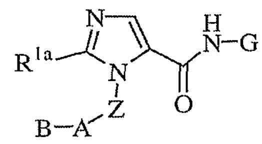

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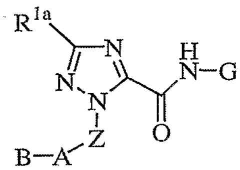

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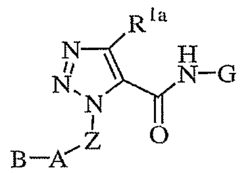

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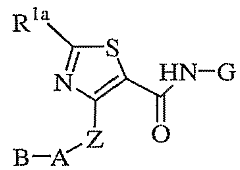

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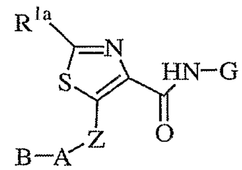

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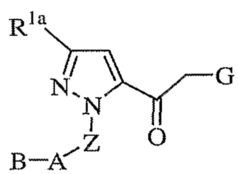

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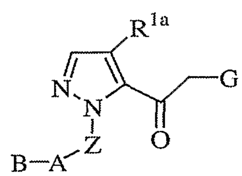

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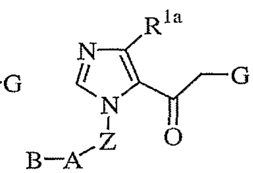

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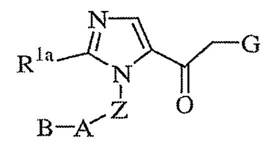

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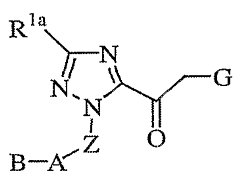

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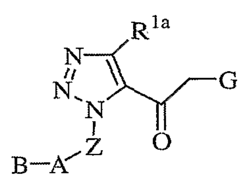

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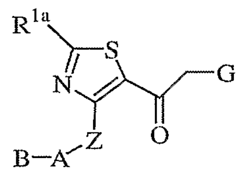

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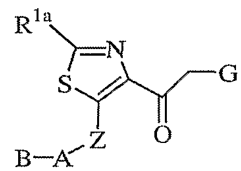

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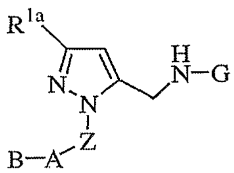

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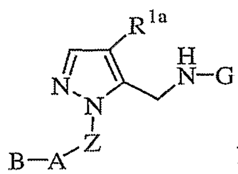

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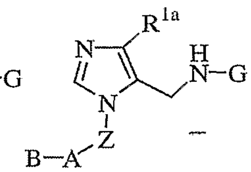

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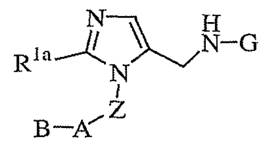

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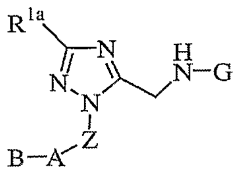

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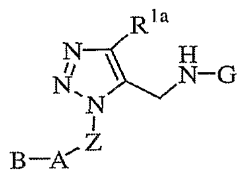

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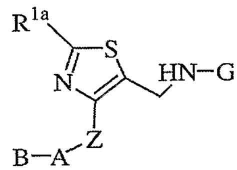

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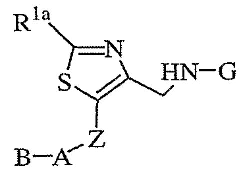

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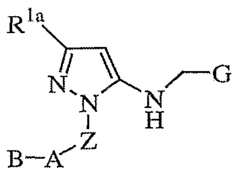

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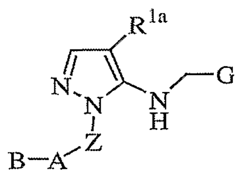

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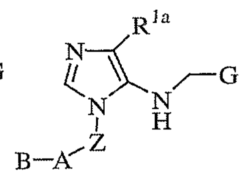

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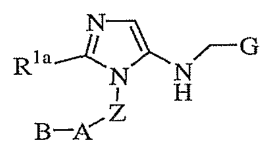

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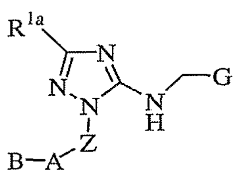

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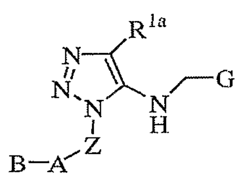

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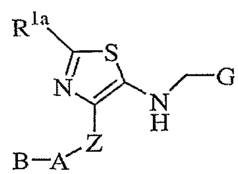

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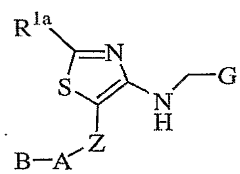

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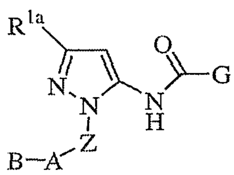
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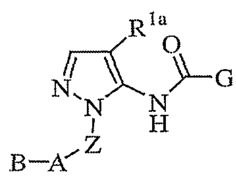
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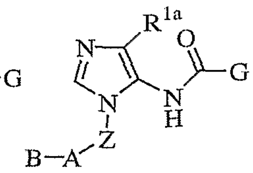
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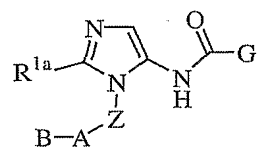
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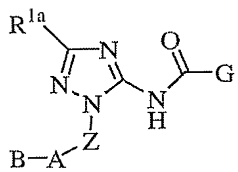
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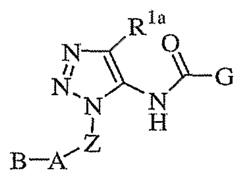
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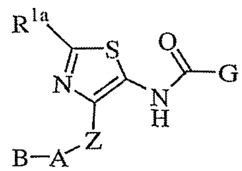
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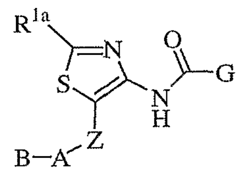
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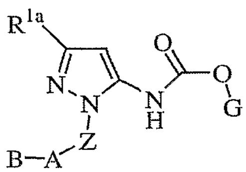
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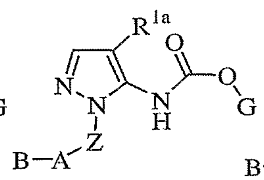
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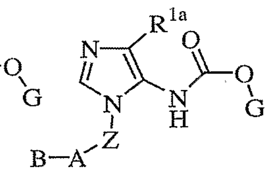
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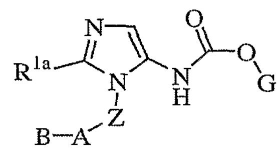
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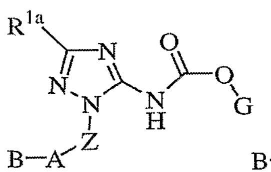
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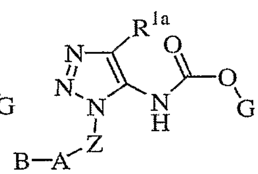
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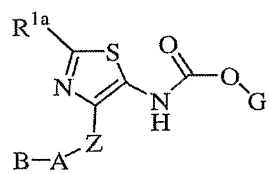
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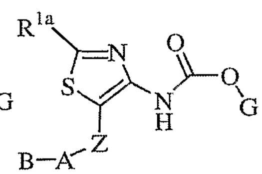
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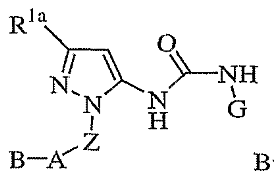

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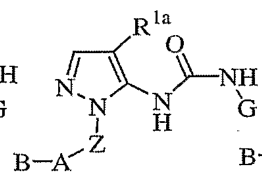

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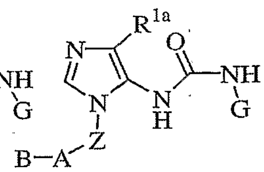

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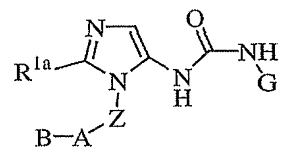

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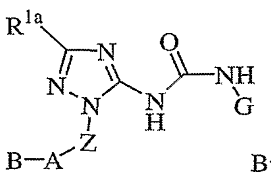

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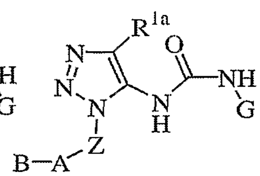

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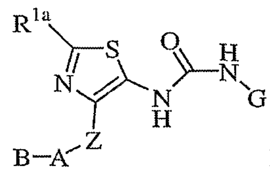

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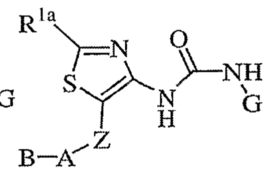

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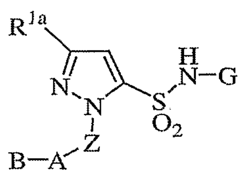

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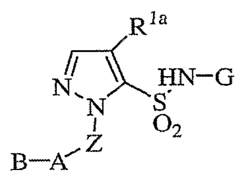

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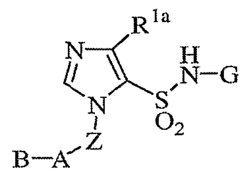

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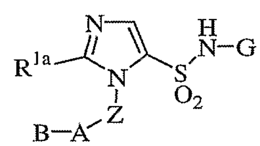

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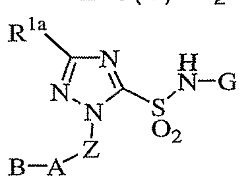

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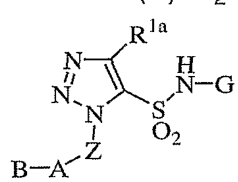

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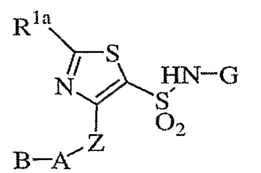

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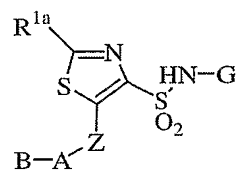

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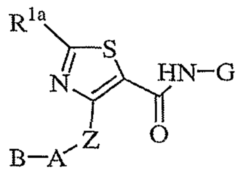

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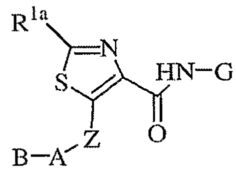

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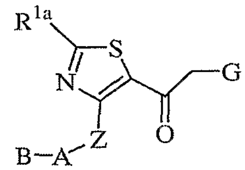

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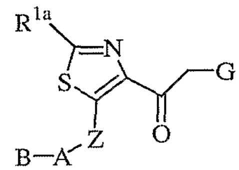

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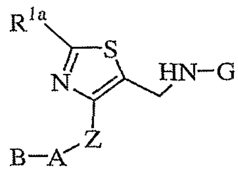

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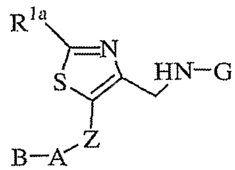

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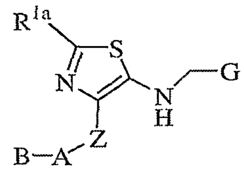

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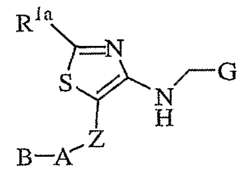

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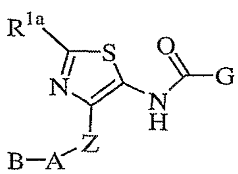

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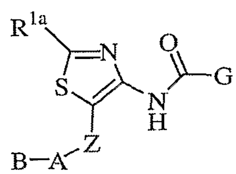

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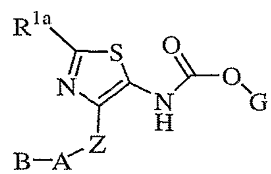

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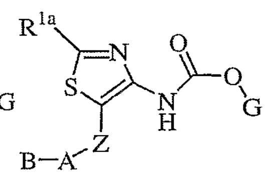

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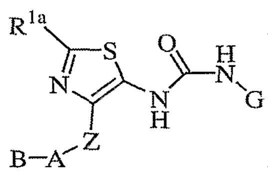

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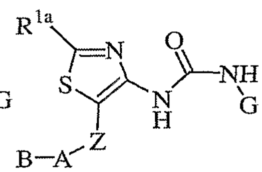

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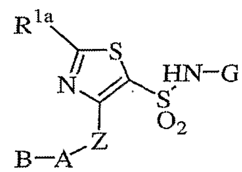

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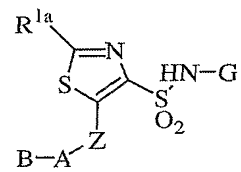


Z=C(O)NH

G is selected from:

4-(methoxy)phenyl;

3-Cl-phenyl;

4-F-3-Cl-phenyl;

3-H_2N-4-Cl-phenyl;

2-(H_2NCH_2)phenyl;

2-(H_2NCH_2)-3-F-phenyl;

2-(H_2NCH_2)-4-F-phenyl;

2-(H_2NCH_2)-5-F-phenyl;

2-(H_2NCH_2)-6-F-phenyl;

3-(amidino)phenyl;

1-($H_2NC(O)$)phenyl;

3-($H_2NC(O)$)phenyl;

1-($H_2NC(O)$)-4-methoxy-phenyl;

4-Cl-pyridin-2-yl;
3-amino-phthalazin-5-yl;
3-amino-phthalazin-6-yl;
1-aminoisoquinolin-7-yl;
4-aminoquinazol-6-yl;
3-aminobenzisoxazol-5-yl; and,
3-aminoindazol-5-yl;

R^{1a} is CH_3;

Ex#	A	B
1.	phenyl	2-(NH_2SO_2)phenyl
2.	phenyl	2-(CH_3SO_2)phenyl
3.	phenyl	3-NH_2SO_2-4-pyridyl
4.	phenyl	3-CH_3SO_2-4-pyridyl
5.	phenyl	2-(CH_3NH)phenyl
6.	phenyl	3-($(CH_3)_2NCH_2$)-4-pyridyl
7.	phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
8.	phenyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
9.	phenyl	2-($(CH_3)_2NCH_2$)phenyl
10.	phenyl	2-($(CH_3)NHCH_2$)phenyl
11.	phenyl	2-($(CH_3CH_2)NHCH_2$)phenyl
12.	phenyl	2-($(CH_3CH_2)_2NCH_2$)phenyl
13.	phenyl	2-($(CH_3CH_2)N(CH_3)CH_2$)phenyl
14.	phenyl	2-($((CH_3)_2CH)NHCH_2$)phenyl
15.	phenyl	2-($((CH_3)_2CH)_2NCH_2$)phenyl
16.	phenyl	2-((cyclopropyl)$NHCH_2$)phenyl
17.	phenyl	2-((cyclopropyl)$_2NCH_2$)phenyl
18.	phenyl	2-((cyclobutyl)$NHCH_2$)phenyl
19.	phenyl	2-((cyclobutyl)$_2NCH_2$)phenyl
20.	phenyl	2-((cyclopentyl)$NHCH_2$)phenyl
21.	phenyl	2-((cyclopentyl)$_2NCH_2$)phenyl
22.	phenyl	2-((cyclohexyl)$NHCH_2$)phenyl
23.	phenyl	2-((cyclohexyl)$_2NCH_2$)phenyl
24.	phenyl	1-CH_3-2-imidazolyl
25.	phenyl	2-CH_3-1-imidazolyl
26.	phenyl	2-($(CH_3)_2NCH_2$)-1-imidazolyl
27.	phenyl	2-($(CH_3)NHCH_2$)-1-imidazolyl
28.	phenyl	2-($(CH_3CH_2)NHCH_2$)-1-imidazolyl
29.	phenyl	2-($(CH_3CH_2)_2NCH_2$)-1-imidazolyl
30.	phenyl	2-($(CH_3CH_2)N(CH_3)CH_2$)-1-imidazolyl
31.	phenyl	2-($((CH_3)_2CH)NHCH_2$)-1-imidazolyl
32.	phenyl	2-($((CH_3)_2CH)_2NCH_2$)-1-imidazolyl
33.	phenyl	2-((cyclopropyl)$NHCH_2$)-1-imidazolyl
34.	phenyl	2-((cyclopropyl)$_2NCH_2$)-1-imidazolyl

35.	phenyl	2-((cyclobutyl)$NHCH_2$)-1-imidazolyl
36.	phenyl	2-((cyclobutyl)$_2NCH_2$)-1-imidazolyl
37.	phenyl	2-((cyclopentyl)$NHCH_2$)-1-imidazolyl
38.	phenyl	2-((cyclopentyl)$_2NCH_2$)-1-imidazolyl
39.	phenyl	2-((cyclohexyl)$NHCH_2$)-1-imidazolyl
40.	phenyl	2-((cyclohexyl)$_2NCH_2$)-1-imidazolyl
41.	2-pyridyl	2-(NH_2SO_2)phenyl
42.	2-pyridyl	2-(CH_3SO_2)phenyl
43.	2-pyridyl	3-NH_2SO_2-4-pyridyl
44.	2-pyridyl	3-CH_3SO_2-4-pyridyl
45.	2-pyridyl	2-(CH_3NH)phenyl
46.	2-pyridyl	3-((CH_3)$_2NCH_2$)-4-pyridyl
47.	2-pyridyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
48.	2-pyridyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
49.	2-pyridyl	2-((CH_3)$_2NCH_2$)phenyl
50.	2-pyridyl	2-((CH_3)$NHCH_2$)phenyl
51.	2-pyridyl	2-((CH_3CH_2)$NHCH_2$)phenyl
52.	2-pyridyl	2-((CH_3CH_2)$_2NCH_2$)phenyl
53.	2-pyridyl	2-((CH_3CH_2)N(CH_3)CH_2)phenyl
54.	2-pyridyl	2-(((CH_3)$_2$CH)$NHCH_2$)phenyl
55.	2-pyridyl	2-(((CH_3)$_2$CH)$_2NCH_2$)phenyl
56.	2-pyridyl	2-((cyclopropyl)$NHCH_2$)phenyl
57.	2-pyridyl	2-((cyclopropyl)$_2NCH_2$)phenyl
58.	2-pyridyl	2-((cyclobutyl)$NHCH_2$)phenyl
59.	2-pyridyl	2-((cyclobutyl)$_2NCH_2$)phenyl
60.	2-pyridyl	2-((cyclopentyl)$NHCH_2$)phenyl
61.	2-pyridyl	2-((cyclopentyl)$_2NCH_2$)phenyl
62.	2-pyridyl	2-((cyclohexyl)$NHCH_2$)phenyl
63.	2-pyridyl	2-((cyclohexyl)$_2NCH_2$)phenyl
64.	2-pyridyl	1-CH_3-2-imidazolyl
65.	2-pyridyl	2-CH_3-1-imidazolyl
66.	2-pyridyl	2-((CH_3)$_2NCH_2$)-1-imidazolyl
67.	2-pyridyl	2-((CH_3)$NHCH_2$)-1-imidazolyl
68.	2-pyridyl	2-((CH_3CH_2)$NHCH_2$)-1-imidazolyl
69.	2-pyridyl	2-((CH_3CH_2)$_2NCH_2$)-1-imidazolyl
70.	2-pyridyl	2-((CH_3CH_2)N(CH_3)CH_2)-1-imidazolyl
71.	2-pyridyl	2-(((CH_3)$_2$CH)$NHCH_2$)-1-imidazolyl
72.	2-pyridyl	2-(((CH_3)$_2$CH)$_2NCH_2$)-1-imidazolyl
73.	2-pyridyl	2-((cyclopropyl)$NHCH_2$)-1-imidazolyl
74.	2-pyridyl	2-((cyclopropyl)$_2NCH_2$)-1-imidazolyl
75.	2-pyridyl	2-((cyclobutyl)$NHCH_2$)-1-imidazolyl
76.	2-pyridyl	2-((cyclobutyl)$_2NCH_2$)-1-imidazolyl
77.	2-pyridyl	2-((cyclopentyl)$NHCH_2$)-1-imidazolyl
78.	2-pyridyl	2-((cyclopentyl)$_2NCH_2$)-1-imidazolyl
79.	2-pyridyl	2-((cyclohexyl)$NHCH_2$)-1-imidazolyl
80.	2-pyridyl	2-((cyclohexyl)$_2NCH_2$)-1-imidazolyl
81.	3-pyridyl	2-(NH_2SO_2)phenyl
82.	3-pyridyl	2-(CH_3SO_2)phenyl
83.	3-pyridyl	3-NH_2SO_2-4-pyridyl
84.	3-pyridyl	3-CH_3SO_2-4-pyridyl

85.	3-pyridyl	2-(CH_3NH)phenyl
86.	3-pyridyl	3-((CH_3)$_2NCH_2$)-4-pyridyl
87.	3-pyridyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
88.	3-pyridyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
89.	3-pyridyl	2-((CH_3)$_2NCH_2$)phenyl
90.	3-pyridyl	2-((CH_3)$NHCH_2$)phenyl
91.	3-pyridyl	2-((CH_3CH_2)$NHCH_2$)phenyl
92.	3-pyridyl	2-((CH_3CH_2)$_2NCH_2$)phenyl
93.	3-pyridyl	2-((CH_3CH_2)N(CH_3)CH_2)phenyl
94.	3-pyridyl	2-(((CH_3)$_2$CH)$NHCH_2$)phenyl
95.	3-pyridyl	2-(((CH_3)$_2$CH)$_2NCH_2$)phenyl
96.	3-pyridyl	2-((cyclopropyl)$NHCH_2$)phenyl
97.	3-pyridyl	2-((cyclopropyl)$_2NCH_2$)phenyl
98.	3-pyridyl	2-((cyclobutyl)$NHCH_2$)phenyl
99.	3-pyridyl	2-((cyclobutyl)$_2NCH_2$)phenyl
100.	3-pyridyl	2-((cyclopentyl)$NHCH_2$)phenyl
101.	3-pyridyl	2-((cyclopentyl)$_2NCH_2$)phenyl
102.	3-pyridyl	2-((cyclohexyl)$NHCH_2$)phenyl
103.	3-pyridyl	2-((cyclohexyl)$_2NCH_2$)phenyl
104.	3-pyridyl	1-CH_3-2-imidazolyl
105.	3-pyridyl	2-CH_3-1-imidazolyl
106.	3-pyridyl	2-((CH_3)$_2NCH_2$)-1-imidazolyl
107.	3-pyridyl	2-((CH_3)$NHCH_2$)-1-imidazolyl
108.	3-pyridyl	2-((CH_3CH_2)$NHCH_2$)-1-imidazolyl
109.	3-pyridyl	2-((CH_3CH_2)$_2NCH_2$)-1-imidazolyl
110.	3-pyridyl	2-((CH_3CH_2)N(CH_3)CH_2)-1-imidazolyl
111.	3-pyridyl	2-(((CH_3)$_2$CH)$NHCH_2$)-1-imidazolyl
112.	3-pyridyl	2-(((CH_3)$_2$CH)$_2NCH_2$)-1-imidazolyl
113.	3-pyridyl	2-((cyclopropyl)$NHCH_2$)-1-imidazolyl
114.	3-pyridyl	2-((cyclopropyl)$_2NCH_2$)-1-imidazolyl
115.	3-pyridyl	2-((cyclobutyl)$NHCH_2$)-1-imidazolyl
116.	3-pyridyl	2-((cyclobutyl)$_2NCH_2$)-1-imidazolyl
117.	3-pyridyl	2-((cyclopentyl)$NHCH_2$)-1-imidazolyl
118.	3-pyridyl	2-((cyclopentyl)$_2NCH_2$)-1-imidazolyl
119.	3-pyridyl	2-((cyclohexyl)$NHCH_2$)-1-imidazolyl
120.	3-pyridyl	2-((cyclohexyl)$_2NCH_2$)-1-imidazolyl
121.	2-pyrimidyl	2-(NH_2SO_2)phenyl
122.	2-pyrimidyl	2-(CH_3SO_2)phenyl
123.	2-pyrimidyl	3-NH_2SO_2-4-pyridyl
124.	2-pyrimidyl	3-CH_3SO_2-4-pyridyl
125.	2-pyrimidyl	2-(CH_3NH)phenyl
126.	2-pyrimidyl	3-((CH_3)$_2NCH_2$)-4-pyridyl
127.	2-pyrimidyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
128.	2-pyrimidyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
129.	2-pyrimidyl	2-((CH_3)$_2NCH_2$)phenyl
130.	2-pyrimidyl	2-((CH_3)$NHCH_2$)phenyl
131.	2-pyrimidyl	2-((CH_3CH_2)$NHCH_2$)phenyl
132.	2-pyrimidyl	2-((CH_3CH_2)$_2NCH_2$)phenyl
133.	2-pyrimidyl	2-((CH_3CH_2)N(CH_3)CH_2)phenyl
134.	2-pyrimidyl	2-(((CH_3)$_2$CH)$NHCH_2$)phenyl

135.	2-pyrimidyl	2-(((CH$_3$)$_2$CH)$_2$NCH$_2$)phenyl
136.	2-pyrimidyl	2-((cyclopropyl)NHCH$_2$)phenyl
137.	2-pyrimidyl	2-((cyclopropyl)$_2$NCH$_2$)phenyl
138.	2-pyrimidyl	2-((cyclobutyl)NHCH$_2$)phenyl
139.	2-pyrimidyl	2-((cyclobutyl)$_2$NCH$_2$)phenyl
140.	2-pyrimidyl	2-((cyclopentyl)NHCH$_2$)phenyl
141.	2-pyrimidyl	2-((cyclopentyl)$_2$NCH$_2$)phenyl
142.	2-pyrimidyl	2-((cyclohexyl)NHCH$_2$)phenyl
143.	2-pyrimidyl	2-((cyclohexyl)$_2$NCH$_2$)phenyl
144.	2-pyrimidyl	1-CH$_3$-2-imidazolyl
145.	2-pyrimidyl	2-CH$_3$-1-imidazolyl
146.	2-pyrimidyl	2-((CH$_3$)$_2$NCH$_2$)-1-imidazolyl
147.	2-pyrimidyl	2-((CH$_3$)NHCH$_2$)-1-imidazolyl
148.	2-pyrimidyl	2-((CH$_3$CH$_2$)NHCH$_2$)-1-imidazolyl
149.	2-pyrimidyl	2-((CH$_3$CH$_2$)$_2$NCH$_2$)-1-imidazolyl
150.	2-pyrimidyl	2-((CH$_3$CH$_2$)N(CH$_3$)CH$_2$)-1-imidazolyl
151.	2-pyrimidyl	2-(((CH$_3$)$_2$CH)NHCH$_2$)-1-imidazolyl
152.	2-pyrimidyl	2-(((CH$_3$)$_2$CH)$_2$NCH$_2$)-1-imidazolyl
153.	2-pyrimidyl	2-((cyclopropyl)NHCH$_2$)-1-imidazolyl
154.	2-pyrimidyl	2-((cyclopropyl)$_2$NCH$_2$)-1-imidazolyl
155.	2-pyrimidyl	2-((cyclobutyl)NHCH$_2$)-1-imidazolyl
156.	2-pyrimidyl	2-((cyclobutyl)$_2$NCH$_2$)-1-imidazolyl
157.	2-pyrimidyl	2-((cyclopentyl)NHCH$_2$)-1-imidazolyl
158.	2-pyrimidyl	2-((cyclopentyl)$_2$NCH$_2$)-1-imidazolyl
159.	2-pyrimidyl	2-((cyclohexyl)NHCH$_2$)-1-imidazolyl
160.	2-pyrimidyl	2-((cyclohexyl)$_2$NCH$_2$)-1-imidazolyl
161.	5-pyrimidyl	2-(NH$_2$SO$_2$)phenyl
162.	5-pyrimidyl	2-(CH$_3$SO$_2$)phenyl
163.	5-pyrimidyl	3-NH$_2$SO$_2$-4-pyridyl
164.	5-pyrimidyl	3-CH$_3$SO$_2$-4-pyridyl
165.	5-pyrimidyl	2-(CH$_3$NH)phenyl
166.	5-pyrimidyl	3-((CH$_3$)$_2$NCH$_2$)-4-pyridyl
167.	5-pyrimidyl	2-(N-(3-R-HO-pyrrolidinyl)CH$_2$)phenyl
168.	5-pyrimidyl	2-(N-(4-HO-piperidinyl)CH$_2$)phenyl
169.	5-pyrimidyl	2-((CH$_3$)$_2$NCH$_2$)phenyl
170.	5-pyrimidyl	2-((CH$_3$)NHCH$_2$)phenyl
171.	5-pyrimidyl	2-((CH$_3$CH$_2$)NHCH$_2$)phenyl
172.	5-pyrimidyl	2-((CH$_3$CH$_2$)$_2$NCH$_2$)phenyl
173.	5-pyrimidyl	2-((CH$_3$CH$_2$)N(CH$_3$)CH$_2$)phenyl
174.	5-pyrimidyl	2-(((CH$_3$)$_2$CH)NHCH$_2$)phenyl
175.	5-pyrimidyl	2-(((CH$_3$)$_2$CH)$_2$NCH$_2$)phenyl
176.	5-pyrimidyl	2-((cyclopropyl)NHCH$_2$)phenyl
177.	5-pyrimidyl	2-((cyclopropyl)$_2$NCH$_2$)phenyl
178.	5-pyrimidyl	2-((cyclobutyl)NHCH$_2$)phenyl
179.	5-pyrimidyl	2-((cyclobutyl)$_2$NCH$_2$)phenyl
180.	5-pyrimidyl	2-((cyclopentyl)NHCH$_2$)phenyl
181.	5-pyrimidyl	2-((cyclopentyl)$_2$NCH$_2$)phenyl
182.	5-pyrimidyl	2-((cyclohexyl)NHCH$_2$)phenyl
183.	5-pyrimidyl	2-((cyclohexyl)$_2$NCH$_2$)phenyl
184.	5-pyrimidyl	1-CH$_3$-2-imidazolyl

185.	5-pyrimidyl	$2-CH_3-1$-imidazolyl
186.	5-pyrimidyl	$2-((CH_3)_2NCH_2)-1$-imidazolyl
187.	5-pyrimidyl	$2-((CH_3)NHCH_2)-1$-imidazolyl
188.	5-pyrimidyl	$2-((CH_3CH_2)NHCH_2)-1$-imidazolyl
189.	5-pyrimidyl	$2-((CH_3CH_2)_2NCH_2)-1$-imidazolyl
190.	5-pyrimidyl	$2-((CH_3CH_2)N(CH_3)CH_2)-1$-imidazolyl
191.	5-pyrimidyl	$2-(((CH_3)_2CH)NHCH_2)-1$-imidazolyl
192.	5-pyrimidyl	$2-(((CH_3)_2CH)_2NCH_2)-1$-imidazolyl
193.	5-pyrimidyl	2-((cyclopropyl)$NHCH_2$)-1-imidazolyl
194.	5-pyrimidyl	2-((cyclopropyl)$_2NCH_2$)-1-imidazolyl
195.	5-pyrimidyl	2-((cyclobutyl)$NHCH_2$)-1-imidazolyl
196.	5-pyrimidyl	2-((cyclobutyl)$_2NCH_2$)-1-imidazolyl
197.	5-pyrimidyl	2-((cyclopentyl)$NHCH_2$)-1-imidazolyl
198.	5-pyrimidyl	2-((cyclopentyl)$_2NCH_2$)-1-imidazolyl
199.	5-pyrimidyl	2-((cyclohexyl)$NHCH_2$)-1-imidazolyl
200.	5-pyrimidyl	2-((cyclohexyl)$_2NCH_2$)-1-imidazolyl
201.	2-Cl-phenyl	$2-(NH_2SO_2)$phenyl
202.	2-Cl-phenyl	$2-(CH_3SO_2)$phenyl
203.	2-Cl-phenyl	$3-NH_2SO_2-4$-pyridyl
204.	2-Cl-phenyl	$3-CH_3SO_2-4$-pyridyl
205.	2-Cl-phenyl	$2-(CH_3NH)$phenyl
206.	2-Cl-phenyl	$3-((CH_3)_2NCH_2)-4$-pyridyl
207.	2-Cl-phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
208.	2-Cl-phenyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
209.	2-Cl-phenyl	$2-((CH_3)_2NCH_2)$phenyl
210.	2-Cl-phenyl	$2-((CH_3)NHCH_2)$phenyl
211.	2-Cl-phenyl	$2-((CH_3CH_2)NHCH_2)$phenyl
212.	2-Cl-phenyl	$2-((CH_3CH_2)_2NCH_2)$phenyl
213.	2-Cl-phenyl	$2-((CH_3CH_2)N(CH_3)CH_2)$phenyl
214.	2-Cl-phenyl	$2-(((CH_3)_2CH)NHCH_2)$phenyl
215.	2-Cl-phenyl	$2-(((CH_3)_2CH)_2NCH_2)$phenyl
216.	2-Cl-phenyl	2-((cyclopropyl)$NHCH_2$)phenyl
217.	2-Cl-phenyl	2-((cyclopropyl)$_2NCH_2$)phenyl
218.	2-Cl-phenyl	2-((cyclobutyl)$NHCH_2$)phenyl
219.	2-Cl-phenyl	2-((cyclobutyl)$_2NCH_2$)phenyl
220.	2-Cl-phenyl	2-((cyclopentyl)$NHCH_2$)phenyl
221.	2-Cl-phenyl	2-((cyclopentyl)$_2NCH_2$)phenyl
222.	2-Cl-phenyl	2-((cyclohexyl)$NHCH_2$)phenyl
223.	2-Cl-phenyl	2-((cyclohexyl)$_2NCH_2$)phenyl
224.	2-Cl-phenyl	$1-CH_3-2$-imidazolyl
225.	2-Cl-phenyl	$2-CH_3-1$-imidazolyl
226.	2-Cl-phenyl	$2-((CH_3)_2NCH_2)-1$-imidazolyl
227.	2-Cl-phenyl	$2-((CH_3)NHCH_2)-1$-imidazolyl
228.	2-Cl-phenyl	$2-((CH_3CH_2)NHCH_2)-1$-imidazolyl
229.	2-Cl-phenyl	$2-((CH_3CH_2)_2NCH_2)-1$-imidazolyl
230.	2-Cl-phenyl	$2-((CH_3CH_2)N(CH_3)CH_2)-1$-imidazolyl
231.	2-Cl-phenyl	$2-(((CH_3)_2CH)NHCH_2)-1$-imidazolyl
232.	2-Cl-phenyl	$2-(((CH_3)_2CH)_2NCH_2)-1$-imidazolyl
233.	2-Cl-phenyl	2-((cyclopropyl)$NHCH_2$)-1-imidazolyl
234.	2-Cl-phenyl	2-((cyclopropyl)$_2NCH_2$)-1-imidazolyl

235.	2-Cl-phenyl	2-((cyclobutyl)$NHCH_2$)-1-imidazolyl
236.	2-Cl-phenyl	2-((cyclobutyl)$_2NCH_2$)-1-imidazolyl
237.	2-Cl-phenyl	2-((cyclopentyl)$NHCH_2$)-1-imidazolyl
238.	2-Cl-phenyl	2-((cyclopentyl)$_2NCH_2$)-1-imidazolyl
239.	2-Cl-phenyl	2-((cyclohexyl)$NHCH_2$)-1-imidazolyl
240.	2-Cl-phenyl	2-((cyclohexyl)$_2NCH_2$)-1-imidazolyl
241.	2-F-phenyl	2-(NH_2SO_2)phenyl
242.	2-F-phenyl	2-(CH_3SO_2)phenyl
243.	2-F-phenyl	3-NH_2SO_2-4-pyridyl
244.	2-F-phenyl	3-CH_3SO_2-4-pyridyl
245.	2-F-phenyl	2-(CH_3NH)phenyl
246.	2-F-phenyl	3-((CH_3)$_2NCH_2$)-4-pyridyl
247.	2-F-phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
248.	2-F-phenyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
249.	2-F-phenyl	2-((CH_3)$_2NCH_2$)phenyl
250.	2-F-phenyl	2-((CH_3)$NHCH_2$)phenyl
251.	2-F-phenyl	2-((CH_3CH_2)$NHCH_2$)phenyl
252.	2-F-phenyl	2-((CH_3CH_2)$_2NCH_2$)phenyl
253.	2-F-phenyl	2-((CH_3CH_2)N(CH_3)CH_2)phenyl
254.	2-F-phenyl	2-(((CH_3)$_2CH$)$NHCH_2$)phenyl
255.	2-F-phenyl	2-(((CH_3)$_2CH$)$_2NCH_2$)phenyl
256.	2-F-phenyl	2-((cyclopropyl)$NHCH_2$)phenyl
257.	2-F-phenyl	2-((cyclopropyl)$_2NCH_2$)phenyl
258.	2-F-phenyl	2-((cyclobutyl)$NHCH_2$)phenyl
259.	2-F-phenyl	2-((cyclobutyl)$_2NCH_2$)phenyl
260.	2-F-phenyl	2-((cyclopentyl)$NHCH_2$)phenyl
261.	2-F-phenyl	2-((cyclopentyl)$_2NCH_2$)phenyl
262.	2-F-phenyl	2-((cyclohexyl)$NHCH_2$)phenyl
263.	2-F-phenyl	2-((cyclohexyl)$_2NCH_2$)phenyl
264.	2-F-phenyl	1-CH_3-2-imidazolyl
265.	2-F-phenyl	2-CH_3-1-imidazolyl
266.	2-F-phenyl	2-((CH_3)$_2NCH_2$)-1-imidazolyl
267.	2-F-phenyl	2-((CH_3)$NHCH_2$)-1-imidazolyl
268.	2-F-phenyl	2-((CH_3CH_2)$NHCH_2$)-1-imidazolyl
269.	2-F-phenyl	2-((CH_3CH_2)$_2NCH_2$)-1-imidazolyl
270.	2-F-phenyl	2-((CH_3CH_2)N(CH_3)CH_2)-1-imidazolyl
271.	2-F-phenyl	2-(((CH_3)$_2CH$)$NHCH_2$)-1-imidazolyl
272.	2-F-phenyl	2-(((CH_3)$_2CH$)$_2NCH_2$)-1-imidazolyl
273.	2-F-phenyl	2-((cyclopropyl)$NHCH_2$)-1-imidazolyl
274.	2-F-phenyl	2-((cyclopropyl)$_2NCH_2$)-1-imidazolyl
275.	2-F-phenyl	2-((cyclobutyl)$NHCH_2$)-1-imidazolyl
276.	2-F-phenyl	2-((cyclobutyl)$_2NCH_2$)-1-imidazolyl
277.	2-F-phenyl	2-((cyclopentyl)$NHCH_2$)-1-imidazolyl
278.	2-F-phenyl	2-((cyclopentyl)$_2NCH_2$)-1-imidazolyl
279.	2-F-phenyl	2-((cyclohexyl)$NHCH_2$)-1-imidazolyl
280.	2-F-phenyl	2-((cyclohexyl)$_2NCH_2$)-1-imidazolyl
281.	2,6-diF-phenyl	2-(NH_2SO_2)phenyl
282.	2,6-diF-phenyl	2-(CH_3SO_2)phenyl
283.	2,6-diF-phenyl	3-NH_2SO_2-4-pyridyl
284.	2,6-diF-phenyl	3-CH_3SO_2-4-pyridyl

285.	2,6-diF-phenyl	2-(CH_3NH)phenyl
286.	2,6-diF-phenyl	3-((CH_3)$_2NCH_2$)-4-pyridyl
287.	2,6-diF-phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
288.	2,6-diF-phenyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
289.	2,6-diF-phenyl	2-((CH_3)$_2NCH_2$)phenyl
290.	2,6-diF-phenyl	2-((CH_3)$NHCH_2$)phenyl
291.	2,6-diF-phenyl	2-((CH_3CH_2)$NHCH_2$)phenyl
292.	2,6-diF-phenyl	2-((CH_3CH_2)$_2NCH_2$)phenyl
293.	2,6-diF-phenyl	2-((CH_3CH_2)N(CH_3)CH_2)phenyl
294.	2,6-diF-phenyl	2-(((CH_3)$_2CH$)$NHCH_2$)phenyl
295.	2,6-diF-phenyl	2-(((CH_3)$_2CH$)$_2NCH_2$)phenyl
296.	2,6-diF-phenyl	2-((cyclopropyl)$NHCH_2$)phenyl
297.	2,6-diF-phenyl	2-((cyclopropyl)$_2NCH_2$)phenyl
298.	2,6-diF-phenyl	2-((cyclobutyl)$NHCH_2$)phenyl
299.	2,6-diF-phenyl	2-((cyclobutyl)$_2NCH_2$)phenyl
300.	2,6-diF-phenyl	2-((cyclopentyl)$NHCH_2$)phenyl
301.	2,6-diF-phenyl	2-((cyclopentyl)$_2NCH_2$)phenyl
302.	2,6-diF-phenyl	2-((cyclohexyl)$NHCH_2$)phenyl
303.	2,6-diF-phenyl	2-((cyclohexyl)$_2NCH_2$)phenyl
304.	2,6-diF-phenyl	1-CH_3-2-imidazolyl
305.	2,6-diF-phenyl	2-CH_3-1-imidazolyl
306.	2,6-diF-phenyl	2-((CH_3)$_2NCH_2$)-1-imidazolyl
307.	2,6-diF-phenyl	2-((CH_3)$NHCH_2$)-1-imidazolyl
308.	2,6-diF-phenyl	2-((CH_3CH_2)$NHCH_2$)-1-imidazolyl
309.	2,6-diF-phenyl	2-((CH_3CH_2)$_2NCH_2$)-1-imidazolyl
310.	2,6-diF-phenyl	2-((CH_3CH_2)N(CH_3)CH_2)-1-imidazolyl
311.	2,6-diF-phenyl	2-(((CH_3)$_2CH$)$NHCH_2$)-1-imidazolyl
312.	2,6-diF-phenyl	2-(((CH_3)$_2CH$)$_2NCH_2$)-1-imidazolyl
313.	2,6-diF-phenyl	2-((cyclopropyl)$NHCH_2$)-1-imidazolyl
314.	2,6-diF-phenyl	2-((cyclopropyl)$_2NCH_2$)-1-imidazolyl
315.	2,6-diF-phenyl	2-((cyclobutyl)$NHCH_2$)-1-imidazolyl
316.	2,6-diF-phenyl	2-((cyclobutyl)$_2NCH_2$)-1-imidazolyl
317.	2,6-diF-phenyl	2-((cyclopentyl)$NHCH_2$)-1-imidazolyl
318.	2,6-diF-phenyl	2-((cyclopentyl)$_2NCH_2$)-1-imidazolyl
319.	2,6-diF-phenyl	2-((cyclohexyl)$NHCH_2$)-1-imidazolyl
320.	2,6-diF-phenyl	2-((cyclohexyl)$_2NCH_2$)-1-imidazolyl
321.	piperidinyl	2-(NH_2SO_2)phenyl
322.	piperidinyl	2-(CH_3SO_2)phenyl
323.	piperidinyl	3-NH_2SO_2-4-pyridyl
324.	piperidinyl	3-CH_3SO_2-4-pyridyl
325.	piperidinyl	2-(CH_3NH)phenyl
326.	piperidinyl	3-((CH_3)$_2NCH_2$)-4-pyridyl
327.	piperidinyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
328.	piperidinyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
329.	piperidinyl	2-((CH_3)$_2NCH_2$)phenyl
330.	piperidinyl	2-((CH_3)$NHCH_2$)phenyl
331.	piperidinyl	2-((CH_3CH_2)$NHCH_2$)phenyl
332.	piperidinyl	2-((CH_3CH_2)$_2NCH_2$)phenyl
333.	piperidinyl	2-((CH_3CH_2)N(CH_3)CH_2)phenyl
334.	piperidinyl	2-(((CH_3)$_2CH$)$NHCH_2$)phenyl

335.	piperidinyl	2-(((CH_3)$_2$CH)$_2$NCH_2)phenyl
336.	piperidinyl	2-((cyclopropyl)NHCH_2)phenyl
337.	piperidinyl	2-((cyclopropyl)$_2$NCH_2)phenyl
338.	piperidinyl	2-((cyclobutyl)NHCH_2)phenyl
339.	piperidinyl	2-((cyclobutyl)$_2$NCH_2)phenyl
340.	piperidinyl	2-((cyclopentyl)NHCH_2)phenyl
341.	piperidinyl	2-((cyclopentyl)$_2$NCH_2)phenyl
342.	piperidinyl	2-((cyclohexyl)NHCH_2)phenyl
343.	piperidinyl	2-((cyclohexyl)$_2$NCH_2)phenyl
344.	piperidinyl	1-CH_3-2-imidazolyl
345.	piperidinyl	2-CH_3-1-imidazolyl
346.	piperidinyl	2-((CH_3)$_2$NCH_2)-1-imidazolyl
347.	piperidinyl	2-((CH_3)NHCH_2)-1-imidazolyl
348.	piperidinyl	2-((CH_3CH_2)NHCH_2)-1-imidazolyl
349.	piperidinyl	2-((CH_3CH_2)$_2$NCH_2)-1-imidazolyl
350.	piperidinyl	2-((CH_3CH_2)N(CH_3)CH_2)-1-imidazolyl
351.	piperidinyl	2-(((CH_3)$_2$CH)NHCH_2)-1-imidazolyl
352.	piperidinyl	2-(((CH_3)$_2$CH)$_2$NCH_2)-1-imidazolyl
353.	piperidinyl	2-((cyclopropyl)NHCH_2)-1-imidazolyl
354.	piperidinyl	2-((cyclopropyl)$_2$NCH_2)-1-imidazolyl
355.	piperidinyl	2-((cyclobutyl)NHCH_2)-1-imidazolyl
356.	piperidinyl	2-((cyclobutyl)$_2$NCH_2)-1-imidazolyl
357.	piperidinyl	2-((cyclopentyl)NHCH_2)-1-imidazolyl
358.	piperidinyl	2-((cyclopentyl)$_2$NCH_2)-1-imidazolyl
359.	piperidinyl	2-((cyclohexyl)NHCH_2)-1-imidazolyl
360.	piperidinyl	2-((cyclohexyl)$_2$NCH_2)-1-imidazolyl
361.	piperidinyl	isopropyl

Table 2

Examples 1-361 use the structures from Table 1 and the corresponding A and B groups from Examples 1-361 of Table 1, and:

R^{1a} is CH_2CH_3.

Table 3

Examples 1-361 use the structures from Table 1 and the corresponding A and B groups from Examples 1-361 of Table 1, and:

R^{1a} is CF_3.

Table 4

Examples 1-361 use the structures from Table 1 and the corresponding A and B groups from Examples 1-361 of Table 1, and:

R^{1a} is SCH_3.

Table 5

Examples 1-361 use the structures from Table 1 and the corresponding A and B groups from Examples 1-361 of Table 1, and:

R^{1a} is $SOCH_3$.

Table 6

Examples 1-361 use the structures from Table 1 and the corresponding A and B groups from Examples 1-361 of Table 1, and:

R^{1a} is SO_2CH_3.

Table 7

Examples 1-361 use the structures from Table 1 and the corresponding A and B groups from Examples 1-361 of Table 1, and:

R^{1a} is Cl.

Table 8

Examples 1-361 use the structures from Table 1 and the corresponding A and B groups from Examples 1-361 of Table 1, and:

R^{1a} is F.

Table 9

Examples 1-361 use the structures from Table 1 and the corresponding A and B groups from Examples 1-361 of Table 1, and:

R^{1a} is CO_2CH_3.

Table 10

Examples 1-361 use the structures from Table 1 and the corresponding A and B groups from Examples 1-361 of Table 1, and:

R^{1a} is CH_2OCH_3.

Table 11

Examples 1-361 use the structures from Table 1 and the corresponding A and B groups from Examples 1-361 of Table 1, and:

R^{1a} is $CONH_2$.

Table 12

Examples 1-361 use the structures from Table 1 and the corresponding A and B groups from Examples 1-361 of Table 1, and:

R^{1a} is CN.

Table 13

Examples 1-361 use the structures from Table 1 and the corresponding A and B groups from Examples 1-361 of Table 1, and:

R^{1a} is CH_2NH_2.

Table 14

Examples 1-361 use the structures from Table 1 and the corresponding A and B groups from Examples 1-361 of Table 1, and:

R^{1a} is $CH_2NHSO_2CH_3$.

Table 15

Examples 1-361 use the structures from Table 1 and the corresponding A and B groups from Examples 1-361 of Table 1, and:

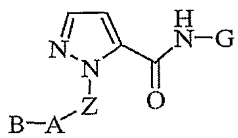
R^{1a} is 1-imidazolyl-CH_2.

Table 16

Examples 1-361 use the structures from Table 1 and the corresponding A and B groups from Examples 1-361 of Table 1, and:

R^{1a} is 1-tetrazolyl-CH_2-.

Table 17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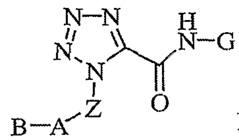
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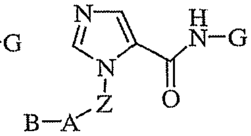
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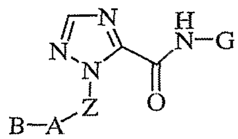
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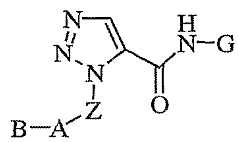
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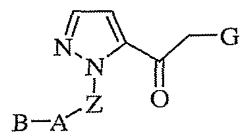
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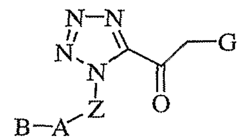
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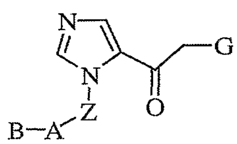
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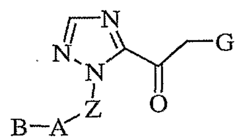
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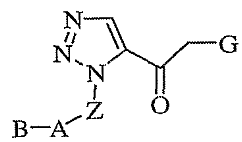
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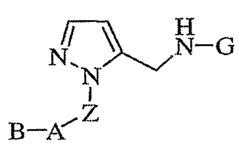
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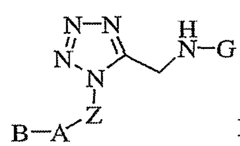
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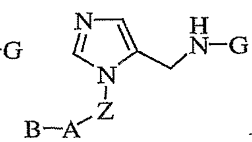
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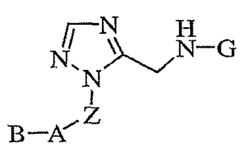
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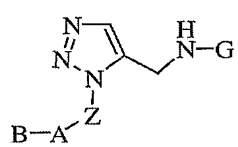
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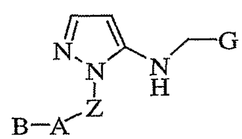
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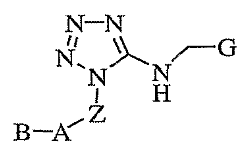
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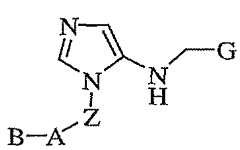
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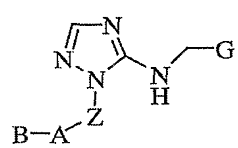
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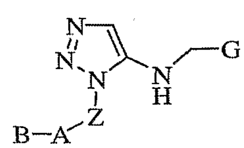
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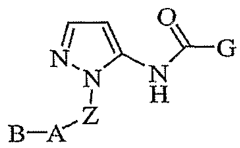
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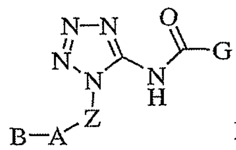
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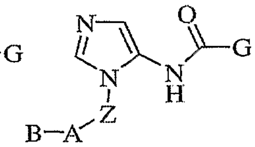
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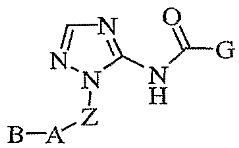
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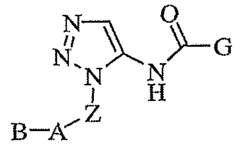
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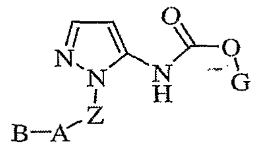
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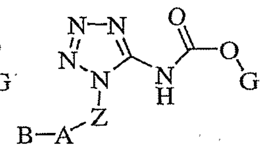
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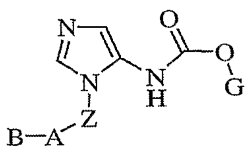
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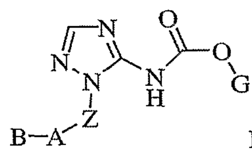
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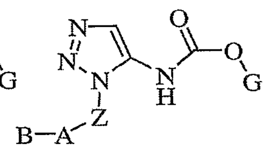
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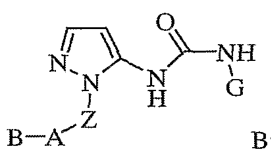
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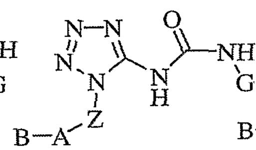
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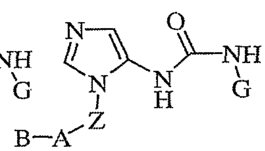
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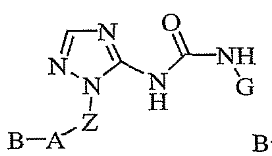
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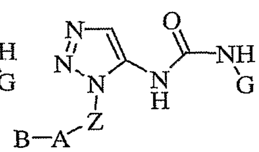
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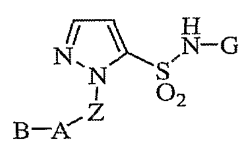
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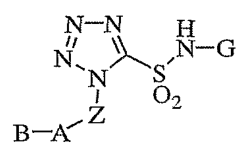
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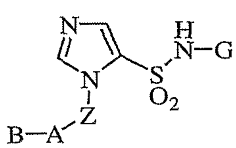
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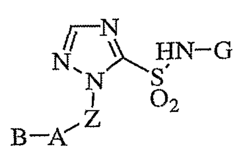
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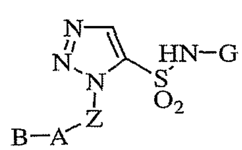
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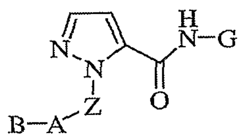
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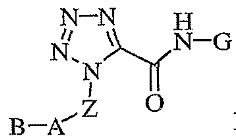
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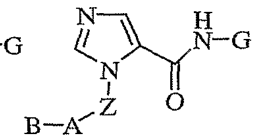
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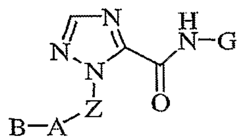
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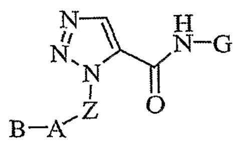
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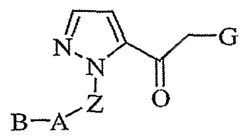
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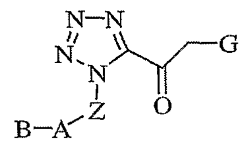
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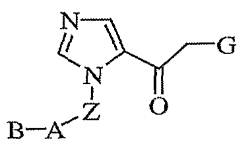
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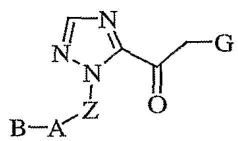
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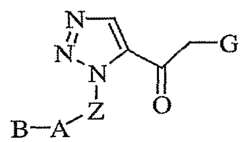
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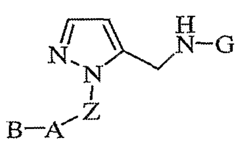
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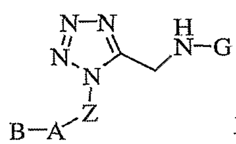
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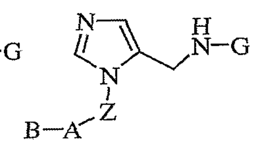
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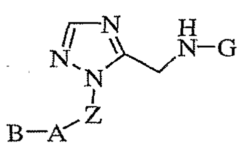
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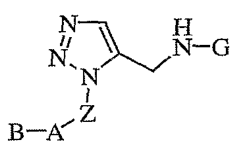
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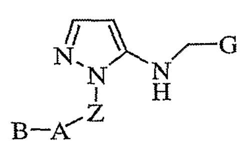
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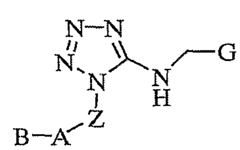
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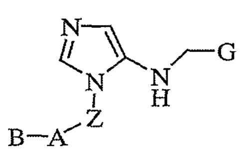
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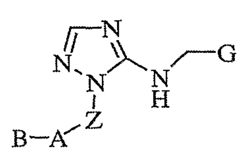
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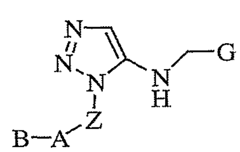
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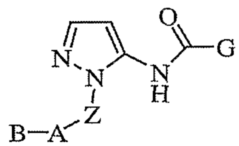
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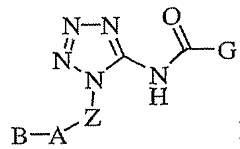
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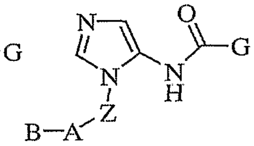
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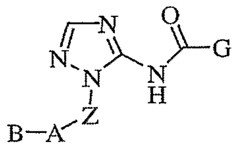
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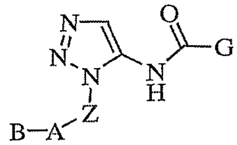
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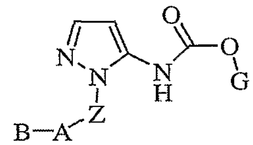
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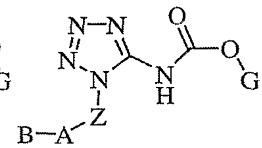
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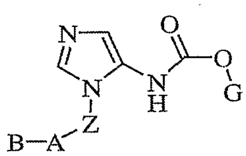
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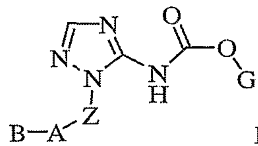
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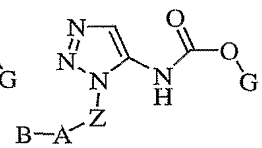
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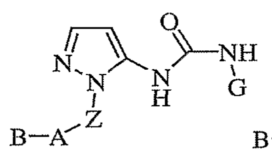
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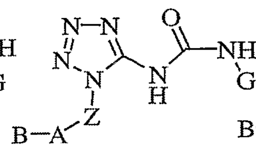
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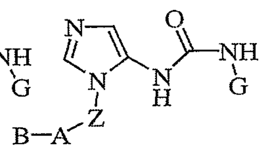
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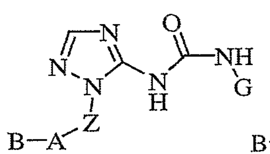
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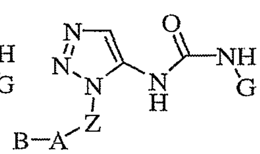
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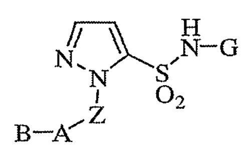
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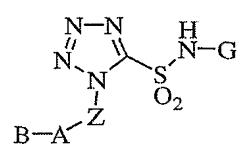
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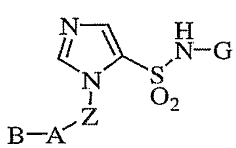
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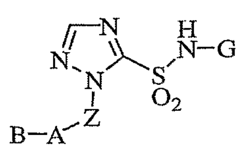
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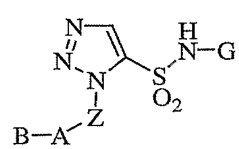
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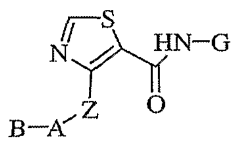
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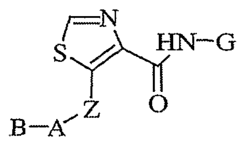
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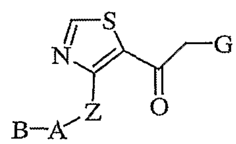
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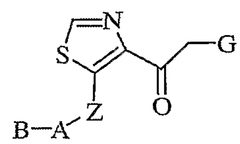
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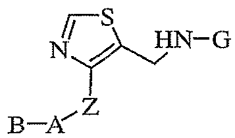
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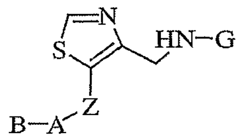
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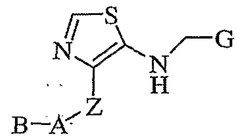
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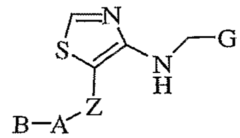
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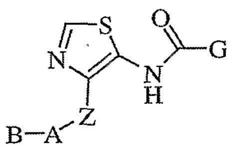
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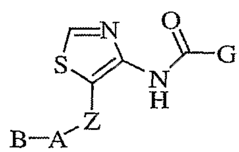
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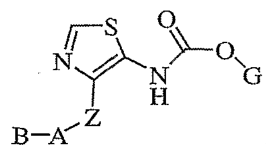
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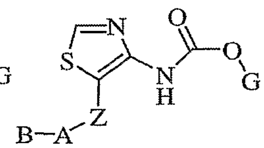
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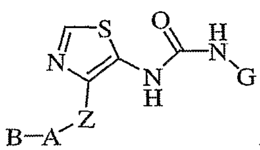
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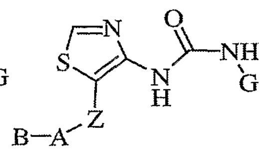
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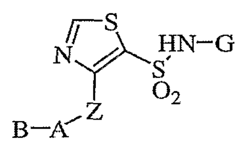
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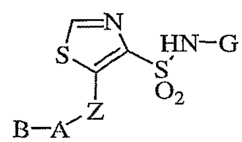
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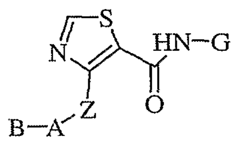
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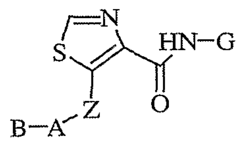
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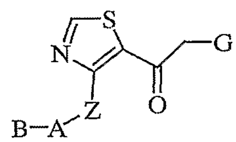
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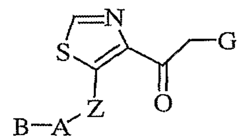
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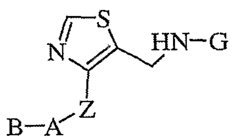
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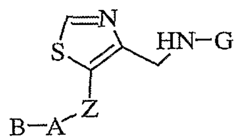
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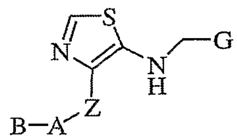
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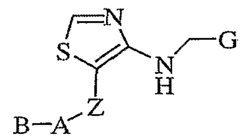
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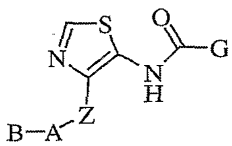
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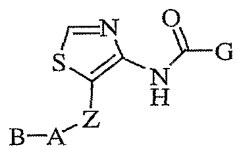
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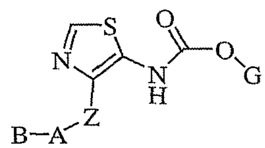
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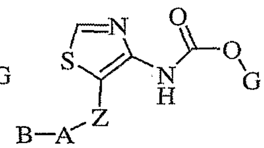
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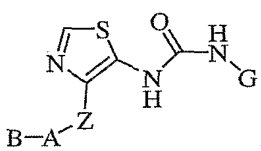
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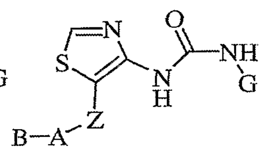
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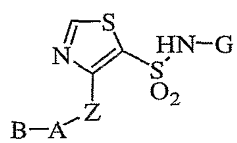
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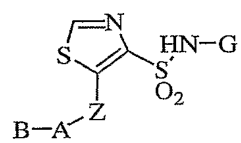
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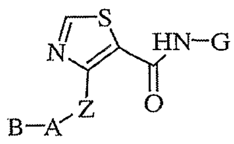
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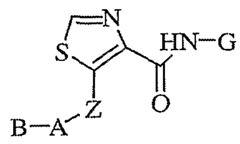
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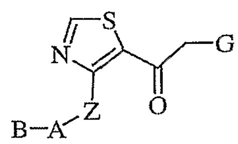
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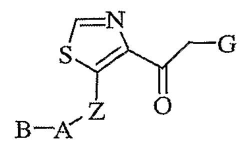
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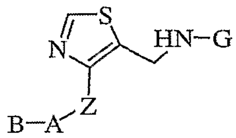
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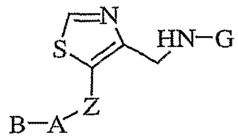
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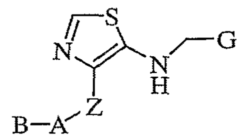
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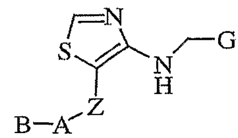
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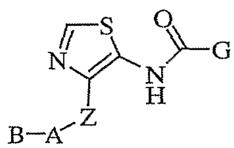
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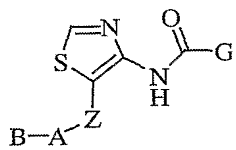
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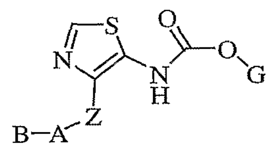
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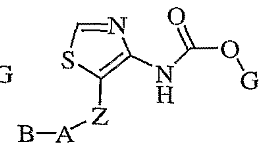
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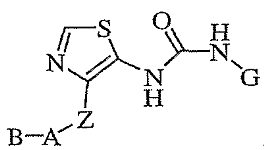
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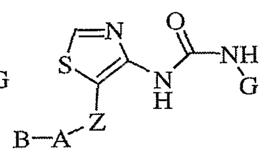
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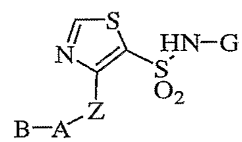
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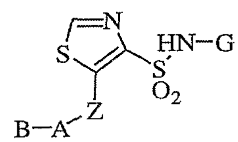
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G is selected from:

4-(methoxy)phenyl;
3-Cl-phenyl;
4-F-3-Cl-phenyl;
3-H_2N-4-Cl-phenyl;
2-(H_2NCH_2)phenyl;
2-(H_2NCH_2)-3-F-phenyl;
2-(H_2NCH_2)-4-F-phenyl;
2-(H_2NCH_2)-5-F-phenyl;
2-(H_2NCH_2)-6-F-phenyl;
3-(amidino)phenyl;
1-($H_2NC(O)$)phenyl;
3-($H_2NC(O)$)phenyl;
1-($H_2NC(O)$)-4-methoxy-phenyl;
4-Cl-pyridin-2-yl;

3-amino-phthalazin-5-yl;

3-amino-phthalazin-6-yl;

1-aminoisoquinolin-7-yl;

4-aminoquinazol-6-yl;

3-aminobenzisoxazol-5-yl; and,

3-aminoindazol-5-yl;

Ex#	A	B
1.	phenyl	2-(NH_2SO_2)phenyl
2.	phenyl	2-(CH_3SO_2)phenyl
3.	phenyl	3-NH_2SO_2-4-pyridyl
4.	phenyl	3-CH_3SO_2-4-pyridyl
5.	phenyl	2-(CH_3NH)phenyl
6.	phenyl	3-($(CH_3)_2NCH_2$)-4-pyridyl
7.	phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
8.	phenyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
9.	phenyl	2-($(CH_3)_2NCH_2$)phenyl
10.	phenyl	2-($(CH_3)NHCH_2$)phenyl
11.	phenyl	2-($(CH_3CH_2)NHCH_2$)phenyl
12.	phenyl	2-($(CH_3CH_2)_2NCH_2$)phenyl
13.	phenyl	2-($(CH_3CH_2)N(CH_3)CH_2$)phenyl
14.	phenyl	2-($((CH_3)_2CH)NHCH_2$)phenyl
15.	phenyl	2-($((CH_3)_2CH)_2NCH_2$)phenyl
16.	phenyl	2-((cyclopropyl)$NHCH_2$)phenyl
17.	phenyl	2-((cyclopropyl)$_2NCH_2$)phenyl
18.	phenyl	2-((cyclobutyl)$NHCH_2$)phenyl
19.	phenyl	2-((cyclobutyl)$_2NCH_2$)phenyl
20.	phenyl	2-((cyclopentyl)$NHCH_2$)phenyl
21.	phenyl	2-((cyclopentyl)$_2NCH_2$)phenyl
22.	phenyl	2-((cyclohexyl)$NHCH_2$)phenyl
23.	phenyl	2-((cyclohexyl)$_2NCH_2$)phenyl
24.	phenyl	1-CH_3-2-imidazolyl
25.	phenyl	2-CH_3-1-imidazolyl
26.	phenyl	2-($(CH_3)_2NCH_2$)-1-imidazolyl
27.	phenyl	2-($(CH_3)NHCH_2$)-1-imidazolyl
28.	phenyl	2-($(CH_3CH_2)NHCH_2$)-1-imidazolyl
29.	phenyl	2-($(CH_3CH_2)_2NCH_2$)-1-imidazolyl
30.	phenyl	2-($(CH_3CH_2)N(CH_3)CH_2$)-1-imidazolyl
31.	phenyl	2-($((CH_3)_2CH)NHCH_2$)-1-imidazolyl
32.	phenyl	2-($((CH_3)_2CH)_2NCH_2$)-1-imidazolyl
33.	phenyl	2-((cyclopropyl)$NHCH_2$)-1-imidazolyl
34.	phenyl	2-((cyclopropyl)$_2NCH_2$)-1-imidazolyl
35.	phenyl	2-((cyclobutyl)$NHCH_2$)-1-imidazolyl
36.	phenyl	2-((cyclobutyl)$_2NCH_2$)-1-imidazolyl
37.	phenyl	2-((cyclopentyl)$NHCH_2$)-1-imidazolyl
38.	phenyl	2-((cyclopentyl)$_2NCH_2$)-1-imidazolyl
39.	phenyl	2-((cyclohexyl)$NHCH_2$)-1-imidazolyl

40.	phenyl	2-((cyclohexyl)$_2$NCH$_2$)-1-imidazolyl
41.	2-pyridyl	2-(NH$_2$SO$_2$)phenyl
42.	2-pyridyl	2-(CH$_3$SO$_2$)phenyl
43.	2-pyridyl	3-NH$_2$SO$_2$-4-pyridyl
44.	2-pyridyl	3-CH$_3$SO$_2$-4-pyridyl
45.	2-pyridyl	2-(CH$_3$NH)phenyl
46.	2-pyridyl	3-((CH$_3$)$_2$NCH$_2$)-4-pyridyl
47.	2-pyridyl	2-(N-(3-R-HO-pyrrolidinyl)CH$_2$)phenyl
48.	2-pyridyl	2-(N-(4-HO-piperidinyl)CH$_2$)phenyl
49.	2-pyridyl	2-((CH$_3$)$_2$NCH$_2$)phenyl
50.	2-pyridyl	2-((CH$_3$)NHCH$_2$)phenyl
51.	2-pyridyl	2-((CH$_3$CH$_2$)NHCH$_2$)phenyl
52.	2-pyridyl	2-((CH$_3$CH$_2$)$_2$NCH$_2$)phenyl
53.	2-pyridyl	2-((CH$_3$CH$_2$)N(CH$_3$)CH$_2$)phenyl
54.	2-pyridyl	2-(((CH$_3$)$_2$CH)NHCH$_2$)phenyl
55.	2-pyridyl	2-(((CH$_3$)$_2$CH)$_2$NCH$_2$)phenyl
56.	2-pyridyl	2-((cyclopropyl)NHCH$_2$)phenyl
57.	2-pyridyl	2-((cyclopropyl)$_2$NCH$_2$)phenyl
58.	2-pyridyl	2-((cyclobutyl)NHCH$_2$)phenyl
59.	2-pyridyl	2-((cyclobutyl)$_2$NCH$_2$)phenyl
60.	2-pyridyl	2-((cyclopentyl)NHCH$_2$)phenyl
61.	2-pyridyl	2-((cyclopentyl)$_2$NCH$_2$)phenyl
62.	2-pyridyl	2-((cyclohexyl)NHCH$_2$)phenyl
63.	2-pyridyl	2-((cyclohexyl)$_2$NCH$_2$)phenyl
64.	2-pyridyl	1-CH$_3$-2-imidazolyl
65.	2-pyridyl	2-CH$_3$-1-imidazolyl
66.	2-pyridyl	2-((CH$_3$)$_2$NCH$_2$)-1-imidazolyl
67.	2-pyridyl	2-((CH$_3$)NHCH$_2$)-1-imidazolyl
68.	2-pyridyl	2-((CH$_3$CH$_2$)NHCH$_2$)-1-imidazolyl
69.	2-pyridyl	2-((CH$_3$CH$_2$)$_2$NCH$_2$)-1-imidazolyl
70.	2-pyridyl	2-((CH$_3$CH$_2$)N(CH$_3$)CH$_2$)-1-imidazolyl
71.	2-pyridyl	2-(((CH$_3$)$_2$CH)NHCH$_2$)-1-imidazolyl
72.	2-pyridyl	2-(((CH$_3$)$_2$CH)$_2$NCH$_2$)-1-imidazolyl
73.	2-pyridyl	2-((cyclopropyl)NHCH$_2$)-1-imidazolyl
74.	2-pyridyl	2-((cyclopropyl)$_2$NCH$_2$)-1-imidazolyl
75.	2-pyridyl	2-((cyclobutyl)NHCH$_2$)-1-imidazolyl
76.	2-pyridyl	2-((cyclobutyl)$_2$NCH$_2$)-1-imidazolyl
77.	2-pyridyl	2-((cyclopentyl)NHCH$_2$)-1-imidazolyl
78.	2-pyridyl	2-((cyclopentyl)$_2$NCH$_2$)-1-imidazolyl
79.	2-pyridyl	2-((cyclohexyl)NHCH$_2$)-1-imidazolyl
80.	2-pyridyl	2-((cyclohexyl)$_2$NCH$_2$)-1-imidazolyl
81.	3-pyridyl	2-(NH$_2$SO$_2$)phenyl
82.	3-pyridyl	2-(CH$_3$SO$_2$)phenyl
83.	3-pyridyl	3-NH$_2$SO$_2$-4-pyridyl
84.	3-pyridyl	3-CH$_3$SO$_2$-4-pyridyl
85.	3-pyridyl	2-(CH$_3$NH)phenyl
86.	3-pyridyl	3-((CH$_3$)$_2$NCH$_2$)-4-pyridyl
87.	3-pyridyl	2-(N-(3-R-HO-pyrrolidinyl)CH$_2$)phenyl
88.	3-pyridyl	2-(N-(4-HO-piperidinyl)CH$_2$)phenyl
89.	3-pyridyl	2-((CH$_3$)$_2$NCH$_2$)phenyl

90.	3-pyridyl	2-((CH_3)$NHCH_2$)phenyl
91.	3-pyridyl	2-((CH_3CH_2)$NHCH_2$)phenyl
92.	3-pyridyl	2-((CH_3CH_2)$_2NCH_2$)phenyl
93.	3-pyridyl	2-((CH_3CH_2)N(CH_3)CH_2)phenyl
94.	3-pyridyl	2-(((CH_3)$_2$CH)$NHCH_2$)phenyl
95.	3-pyridyl	2-(((CH_3)$_2$CH)$_2NCH_2$)phenyl
96.	3-pyridyl	2-((cyclopropyl)$NHCH_2$)phenyl
97.	3-pyridyl	2-((cyclopropyl)$_2NCH_2$)phenyl
98.	3-pyridyl	2-((cyclobutyl)$NHCH_2$)phenyl
99.	3-pyridyl	2-((cyclobutyl)$_2NCH_2$)phenyl
100.	3-pyridyl	2-((cyclopentyl)$NHCH_2$)phenyl
101.	3-pyridyl	2-((cyclopentyl)$_2NCH_2$)phenyl
102.	3-pyridyl	2-((cyclohexyl)$NHCH_2$)phenyl
103.	3-pyridyl	2-((cyclohexyl)$_2NCH_2$)phenyl
104.	3-pyridyl	1-CH_3-2-imidazolyl
105.	3-pyridyl	2-CH_3-1-imidazolyl
106.	3-pyridyl	2-((CH_3)$_2NCH_2$)-1-imidazolyl
107.	3-pyridyl	2-((CH_3)$NHCH_2$)-1-imidazolyl
108.	3-pyridyl	2-((CH_3CH_2)$NHCH_2$)-1-imidazolyl
109.	3-pyridyl	2-((CH_3CH_2)$_2NCH_2$)-1-imidazolyl
110.	3-pyridyl	2-((CH_3CH_2)N(CH_3)CH_2)-1-imidazolyl
111.	3-pyridyl	2-(((CH_3)$_2$CH)$NHCH_2$)-1-imidazolyl
112.	3-pyridyl	2-(((CH_3)$_2$CH)$_2NCH_2$)-1-imidazolyl
113.	3-pyridyl	2-((cyclopropyl)$NHCH_2$)-1-imidazolyl
114.	3-pyridyl	2-((cyclopropyl)$_2NCH_2$)-1-imidazolyl
115.	3-pyridyl	2-((cyclobutyl)$NHCH_2$)-1-imidazolyl
116.	3-pyridyl	2-((cyclobutyl)$_2NCH_2$)-1-imidazolyl
117.	3-pyridyl	2-((cyclopentyl)$NHCH_2$)-1-imidazolyl
118.	3-pyridyl	2-((cyclopentyl)$_2NCH_2$)-1-imidazolyl
119.	3-pyridyl	2-((cyclohexyl)$NHCH_2$)-1-imidazolyl
120.	3-pyridyl	2-((cyclohexyl)$_2NCH_2$)-1-imidazolyl
121.	2-pyrimidyl	2-(NH_2SO_2)phenyl
122.	2-pyrimidyl	2-(CH_3SO_2)phenyl
123.	2-pyrimidyl	3-NH_2SO_2-4-pyridyl
124.	2-pyrimidyl	3-CH_3SO_2-4-pyridyl
125.	2-pyrimidyl	2-(CH_3NH)phenyl
126.	2-pyrimidyl	3-((CH_3)$_2NCH_2$)-4-pyridyl
127.	2-pyrimidyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
128.	2-pyrimidyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
129.	2-pyrimidyl	2-((CH_3)$_2NCH_2$)phenyl
130.	2-pyrimidyl	2-((CH_3)$NHCH_2$)phenyl
131.	2-pyrimidyl	2-((CH_3CH_2)$NHCH_2$)phenyl
132.	2-pyrimidyl	2-((CH_3CH_2)$_2NCH_2$)phenyl
133.	2-pyrimidyl	2-((CH_3CH_2)N(CH_3)CH_2)phenyl
134.	2-pyrimidyl	2-(((CH_3)$_2$CH)$NHCH_2$)phenyl
135.	2-pyrimidyl	2-(((CH_3)$_2$CH)$_2NCH_2$)phenyl
136.	2-pyrimidyl	2-((cyclopropyl)$NHCH_2$)phenyl
137.	2-pyrimidyl	2-((cyclopropyl)$_2NCH_2$)phenyl
138.	2-pyrimidyl	2-((cyclobutyl)$NHCH_2$)phenyl
139.	2-pyrimidyl	2-((cyclobutyl)$_2NCH_2$)phenyl

140.	2-pyrimidyl	2-((cyclopentyl)$NHCH_2$)phenyl
141.	2-pyrimidyl	2-((cyclopentyl)$_2NCH_2$)phenyl
142.	2-pyrimidyl	2-((cyclohexyl)$NHCH_2$)phenyl
143.	2-pyrimidyl	2-((cyclohexyl)$_2NCH_2$)phenyl
144.	2-pyrimidyl	1-CH_3-2-imidazolyl
145.	2-pyrimidyl	2-CH_3-1-imidazolyl
146.	2-pyrimidyl	2-((CH_3)$_2NCH_2$)-1-imidazolyl
147.	2-pyrimidyl	2-((CH_3)$NHCH_2$)-1-imidazolyl
148.	2-pyrimidyl	2-((CH_3CH_2)$NHCH_2$)-1-imidazolyl
149.	2-pyrimidyl	2-((CH_3CH_2)$_2NCH_2$)-1-imidazolyl
150.	2-pyrimidyl	2-((CH_3CH_2)N(CH_3)CH_2)-1-imidazolyl
151.	2-pyrimidyl	2-(((CH_3)$_2$CH)$NHCH_2$)-1-imidazolyl
152.	2-pyrimidyl	2-(((CH_3)$_2$CH)$_2NCH_2$)-1-imidazolyl
153.	2-pyrimidyl	2-((cyclopropyl)$NHCH_2$)-1-imidazolyl
154.	2-pyrimidyl	2-((cyclopropyl)$_2NCH_2$)-1-imidazolyl
155.	2-pyrimidyl	2-((cyclobutyl)$NHCH_2$)-1-imidazolyl
156.	2-pyrimidyl	2-((cyclobutyl)$_2NCH_2$)-1-imidazolyl
157.	2-pyrimidyl	2-((cyclopentyl)$NHCH_2$)-1-imidazolyl
158.	2-pyrimidyl	2-((cyclopentyl)$_2NCH_2$)-1-imidazolyl
159.	2-pyrimidyl	2-((cyclohexyl)$NHCH_2$)-1-imidazolyl
160.	2-pyrimidyl	2-((cyclohexyl)$_2NCH_2$)-1-imidazolyl
161.	5-pyrimidyl	2-(NH_2SO_2)phenyl
162.	5-pyrimidyl	2-(CH_3SO_2)phenyl
163.	5-pyrimidyl	3-NH_2SO_2-4-pyridyl
164.	5-pyrimidyl	3-CH_3SO_2-4-pyridyl
165.	5-pyrimidyl	2-(CH_3NH)phenyl
166.	5-pyrimidyl	3-((CH_3)$_2NCH_2$)-4-pyridyl
167.	5-pyrimidyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
168.	5-pyrimidyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
169.	5-pyrimidyl	2-((CH_3)$_2NCH_2$)phenyl
170.	5-pyrimidyl	2-((CH_3)$NHCH_2$)phenyl
171.	5-pyrimidyl	2-((CH_3CH_2)$NHCH_2$)phenyl
172.	5-pyrimidyl	2-((CH_3CH_2)$_2NCH_2$)phenyl
173.	5-pyrimidyl	2-((CH_3CH_2)N(CH_3)CH_2)phenyl
174.	5-pyrimidyl	2-(((CH_3)$_2$CH)$NHCH_2$)phenyl
175.	5-pyrimidyl	2-(((CH_3)$_2$CH)$_2NCH_2$)phenyl
176.	5-pyrimidyl	2-((cyclopropyl)$NHCH_2$)phenyl
177.	5-pyrimidyl	2-((cyclopropyl)$_2NCH_2$)phenyl
178.	5-pyrimidyl	2-((cyclobutyl)$NHCH_2$)phenyl
179.	5-pyrimidyl	2-((cyclobutyl)$_2NCH_2$)phenyl
180.	5-pyrimidyl	2-((cyclopentyl)$NHCH_2$)phenyl
181.	5-pyrimidyl	2-((cyclopentyl)$_2NCH_2$)phenyl
182.	5-pyrimidyl	2-((cyclohexyl)$NHCH_2$)phenyl
183.	5-pyrimidyl	2-((cyclohexyl)$_2NCH_2$)phenyl
184.	5-pyrimidyl	1-CH_3-2-imidazolyl
185.	5-pyrimidyl	2-CH_3-1-imidazolyl
186.	5-pyrimidyl	2-((CH_3)$_2NCH_2$)-1-imidazolyl
187.	5-pyrimidyl	2-((CH_3)$NHCH_2$)-1-imidazolyl
188.	5-pyrimidyl	2-((CH_3CH_2)$NHCH_2$)-1-imidazolyl
189.	5-pyrimidyl	2-((CH_3CH_2)$_2NCH_2$)-1-imidazolyl

190.	5-pyrimidyl	2-((CH_3CH_2)N(CH_3)CH_2)-1-imidazolyl
191.	5-pyrimidyl	2-(((CH_3)$_2$CH)$NHCH_2$)-1-imidazolyl
192.	5-pyrimidyl	2-(((CH_3)$_2$CH)$_2$$NCH_2$)-1-imidazolyl
193.	5-pyrimidyl	2-((cyclopropyl)$NHCH_2$)-1-imidazolyl
194.	5-pyrimidyl	2-((cyclopropyl)$_2$$NCH_2$)-1-imidazolyl
195.	5-pyrimidyl	2-((cyclobutyl)$NHCH_2$)-1-imidazolyl
196.	5-pyrimidyl	2-((cyclobutyl)$_2$$NCH_2$)-1-imidazolyl
197.	5-pyrimidyl	2-((cyclopentyl)$NHCH_2$)-1-imidazolyl
198.	5-pyrimidyl	2-((cyclopentyl)$_2$$NCH_2$)-1-imidazolyl
199.	5-pyrimidyl	2-((cyclohexyl)$NHCH_2$)-1-imidazolyl
200.	5-pyrimidyl	2-((cyclohexyl)$_2$$NCH_2$)-1-imidazolyl
201.	2-Cl-phenyl	2-(NH_2SO_2)phenyl
202.	2-Cl-phenyl	2-(CH_3SO_2)phenyl
203.	2-Cl-phenyl	3-NH_2SO_2-4-pyridyl
204.	2-Cl-phenyl	3-CH_3SO_2-4-pyridyl
205.	2-Cl-phenyl	2-(CH_3NH)phenyl
206.	2-Cl-phenyl	3-((CH_3)$_2$$NCH_2$)-4-pyridyl
207.	2-Cl-phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH_2)phenyl
208.	2-Cl-phenyl	2-(N-(4-HO-piperidinyl)CH_2)phenyl
209.	2-Cl-phenyl	2-((CH_3)$_2$$NCH_2$)phenyl
210.	2-Cl-phenyl	2-((CH_3)$NHCH_2$)phenyl
211.	2-Cl-phenyl	2-((CH_3CH_2)$NHCH_2$)phenyl
212.	2-Cl-phenyl	2-((CH_3CH_2)$_2$$NCH_2$)phenyl
213.	2-Cl-phenyl	2-((CH_3CH_2)N(CH_3)CH_2)phenyl
214.	2-Cl-phenyl	2-(((CH_3)$_2$CH)$NHCH_2$)phenyl
215.	2-Cl-phenyl	2-(((CH_3)$_2$CH)$_2$$NCH_2$)phenyl
216.	2-Cl-phenyl	2-((cyclopropyl)$NHCH_2$)phenyl
217.	2-Cl-phenyl	2-((cyclopropyl)$_2$$NCH_2$)phenyl
218.	2-Cl-phenyl	2-((cyclobutyl)$NHCH_2$)phenyl
219.	2-Cl-phenyl	2-((cyclobutyl)$_2$$NCH_2$)phenyl
220.	2-Cl-phenyl	2-((cyclopentyl)$NHCH_2$)phenyl
221.	2-Cl-phenyl	2-((cyclopentyl)$_2$$NCH_2$)phenyl
222.	2-Cl-phenyl	2-((cyclohexyl)$NHCH_2$)phenyl
223.	2-Cl-phenyl	2-((cyclohexyl)$_2$$NCH_2$)phenyl
224.	2-Cl-phenyl	1-CH_3-2-imidazolyl
225.	2-Cl-phenyl	2-CH_3-1-imidazolyl
226.	2-Cl-phenyl	2-((CH_3)$_2$$NCH_2$)-1-imidazolyl
227.	2-Cl-phenyl	2-((CH_3)$NHCH_2$)-1-imidazolyl
228.	2-Cl-phenyl	2-((CH_3CH_2)$NHCH_2$)-1-imidazolyl
229.	2-Cl-phenyl	2-((CH_3CH_2)$_2$$NCH_2$)-1-imidazolyl
230.	2-Cl-phenyl	2-((CH_3CH_2)N(CH_3)CH_2)-1-imidazolyl
231.	2-Cl-phenyl	2-(((CH_3)$_2$CH)$NHCH_2$)-1-imidazolyl
232.	2-Cl-phenyl	2-(((CH_3)$_2$CH)$_2$$NCH_2$)-1-imidazolyl
233.	2-Cl-phenyl	2-((cyclopropyl)$NHCH_2$)-1-imidazolyl
234.	2-Cl-phenyl	2-((cyclopropyl)$_2$$NCH_2$)-1-imidazolyl
235.	2-Cl-phenyl	2-((cyclobutyl)$NHCH_2$)-1-imidazolyl
236.	2-Cl-phenyl	2-((cyclobutyl)$_2$$NCH_2$)-1-imidazolyl
237.	2-Cl-phenyl	2-((cyclopentyl)$NHCH_2$)-1-imidazolyl
238.	2-Cl-phenyl	2-((cyclopentyl)$_2$$NCH_2$)-1-imidazolyl
239.	2-Cl-phenyl	2-((cyclohexyl)$NHCH_2$)-1-imidazolyl

240.	2-Cl-phenyl	2-((cyclohexyl)$_2$NCH$_2$)-1-imidazolyl
241.	2-F-phenyl	2-(NH$_2$SO$_2$)phenyl
242.	2-F-phenyl	2-(CH$_3$SO$_2$)phenyl
243.	2-F-phenyl	3-NH$_2$SO$_2$-4-pyridyl
244.	2-F-phenyl	3-CH$_3$SO$_2$-4-pyridyl
245.	2-F-phenyl	2-(CH$_3$NH)phenyl
246.	2-F-phenyl	3-((CH$_3$)$_2$NCH$_2$)-4-pyridyl
247.	2-F-phenyl	2-(N-(3-R-HO-pyrrolidinyl)CH$_2$)phenyl
248.	2-F-phenyl	2-(N-(4-HO-piperidinyl)CH$_2$)phenyl
249.	2-F-phenyl	2-((CH$_3$)$_2$NCH$_2$)phenyl
250.	2-F-phenyl	2-((CH$_3$)NHCH$_2$)phenyl
251.	2-F-phenyl	2-((CH$_3$CH$_2$)NHCH$_2$)phenyl
252.	2-F-phenyl	2-((CH$_3$CH$_2$)$_2$NCH$_2$)phenyl
253.	2-F-phenyl	2-((CH$_3$CH$_2$)N(CH$_3$)CH$_2$)phenyl
254.	2-F-phenyl	2-(((CH$_3$)$_2$CH)NHCH$_2$)phenyl
255.	2-F-phenyl	2-(((CH$_3$)$_2$CH)$_2$NCH$_2$)phenyl
256.	2-F-phenyl	2-((cyclopropyl)NHCH$_2$)phenyl
257.	2-F-phenyl	2-((cyclopropyl)$_2$NCH$_2$)phenyl
258.	2-F-phenyl	2-((cyclobutyl)NHCH$_2$)phenyl
259.	2-F-phenyl	2-((cyclobutyl)$_2$NCH$_2$)phenyl
260.	2-F-phenyl	2-((cyclopentyl)NHCH$_2$)phenyl
261.	2-F-phenyl	2-((cyclopentyl)$_2$NCH$_2$)phenyl
262.	2-F-phenyl	2-((cyclohexyl)NHCH$_2$)phenyl
263.	2-F-phenyl	2-((cyclohexyl)$_2$NCH$_2$)phenyl
264.	2-F-phenyl	1-CH$_3$-2-imidazolyl
265.	2-F-phenyl	2-CH$_3$-1-imidazolyl
266.	2-F-phenyl	2-((CH$_3$)$_2$NCH$_2$)-1-imidazolyl
267.	2-F-phenyl	2-((CH$_3$)NHCH$_2$)-1-imidazolyl
268.	2-F-phenyl	2-((CH$_3$CH$_2$)NHCH$_2$)-1-imidazolyl
269.	2-F-phenyl	2-((CH$_3$CH$_2$)$_2$NCH$_2$)-1-imidazolyl
270.	2-F-phenyl	2-((CH$_3$CH$_2$)N(CH$_3$)CH$_2$)-1-imidazolyl
271.	2-F-phenyl	2-(((CH$_3$)$_2$CH)NHCH$_2$)-1-imidazolyl
272.	2-F-phenyl	2-(((CH$_3$)$_2$CH)$_2$NCH$_2$)-1-imidazolyl
273.	2-F-phenyl	2-((cyclopropyl)NHCH$_2$)-1-imidazolyl
274.	2-F-phenyl	2-((cyclopropyl)$_2$NCH$_2$)-1-imidazolyl
275.	2-F-phenyl	2-((cyclobutyl)NHCH$_2$)-1-imidazolyl
276.	2-F-phenyl	2-((cyclobutyl)$_2$NCH$_2$)-1-imidazolyl
277.	2-F-phenyl	2-((cyclopentyl)NHCH$_2$)-1-imidazolyl

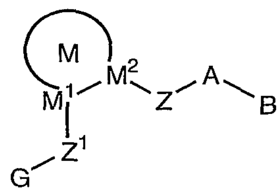
290.	2,6-diF-phenyl	2-((CH$_3$)NHCH$_2$)phenyl
291.	2,6-diF-phenyl	2-((CH$_3$CH$_2$)NHCH$_2$)phenyl
292.	2,6-diF-phenyl	2-((CH$_3$CH$_2$)$_2$NCH$_2$)phenyl
293.	2,6-diF-phenyl	2-((CH$_3$CH$_2$)N(CH$_3$)CH$_2$)phenyl
294.	2,6-diF-phenyl	2-(((CH$_3$)$_2$CH)NHCH$_2$)phenyl
295.	2,6-diF-phenyl	2-(((CH$_3$)$_2$CH)$_2$NCH$_2$)phenyl
296.	2,6-diF-phenyl	2-((cyclopropyl)NHCH$_2$)phenyl
297.	2,6-diF-phenyl	2-((cyclopropyl)$_2$NCH$_2$)phenyl
298.	2,6-diF-phenyl	2-((cyclobutyl)NHCH$_2$)phenyl
299.	2,6-diF-phenyl	2-((cyclobutyl)$_2$NCH$_2$)phenyl
300.	2,6-diF-phenyl	2-((cyclopentyl)NHCH$_2$)phenyl
301.	2,6-diF-phenyl	2-((cyclopentyl)$_2$NCH$_2$)phenyl
302.	2,6-diF-phenyl	2-((cyclohexyl)NHCH$_2$)phenyl
303.	2,6-diF-phenyl	2-((cyclohexyl)$_2$NCH$_2$)phenyl
304.	2,6-diF-phenyl	1-CH$_3$-2-imidazolyl
305.	2,6-diF-phenyl	2-CH$_3$-1-imidazolyl
306.	2,6-diF-phenyl	2-((CH$_3$)$_2$NCH$_2$)-1-imidazolyl
307.	2,6-diF-phenyl	2-((CH$_3$)NHCH$_2$)-1-imidazolyl
308.	2,6-diF-phenyl	2-((CH$_3$CH$_2$)NHCH$_2$)-1-imidazolyl
309.	2,6-diF-phenyl	2-((CH$_3$CH$_2$)$_2$NCH$_2$)-1-imidazolyl
310.	2,6-diF-phenyl	2-((CH$_3$CH$_2$)N(CH$_3$)CH$_2$)-1-imidazolyl
311.	2,6-diF-phenyl	2-(((CH$_3$)$_2$CH)NHCH$_2$)-1-imidazolyl
312.	2,6-diF-phenyl	2-(((CH$_3$)$_2$CH)$_2$NCH$_2$)-1-imidazolyl
313.	2,6-diF-phenyl	2-((cyclopropyl)NHCH$_2$)-1-imidazolyl
314.	2,6-diF-phenyl	2-((cyclopropyl)$_2$NCH$_2$)-1-imidazolyl
315.	2,6-diF-phenyl	2-((cyclobutyl)NHCH$_2$)-1-imidazolyl
316.	2,6-diF-phenyl	2-((cyclobutyl)$_2$NCH$_2$)-1-imidazolyl
317.	2,6-diF-phenyl	2-((cyclopentyl)NHCH$_2$)-1-imidazolyl
318.	2,6-diF-phenyl	2-((cyclopentyl)$_2$NCH$_2$)-1-imidazolyl
319.	2,6-diF-phenyl	2-((cyclohexyl)NHCH$_2$)-1-imidazolyl
320.	2,6-diF-phenyl	2-((cyclohexyl)$_2$NCH$_2$)-1-imidazolyl
321.	piperidinyl	2-(NH$_2$SO$_2$)phenyl
322.	piperidinyl	2-(CH$_3$SO$_2$)phenyl
323.	piperidinyl	3-NH$_2$SO$_2$-4-pyridyl
324.	piperidinyl	3-CH$_3$SO$_2$-4-pyridyl
325.	piperidinyl	2-(CH$_3$NH)phenyl
326.	piperidinyl	3-((CH$_3$)$_2$NCH$_2$)-4-pyridyl
327.	piperidinyl	2-(N-(3-R-HO-pyrrolidinyl)CH$_2$)phenyl
328.	piperidinyl	2-(N-(4-HO-piperidinyl)CH$_2$)phenyl
329.	piperidinyl	2-((CH$_3$)$_2$NCH$_2$)phenyl
330.	piperidinyl	2-((CH$_3$)NHCH$_2$)phenyl
331.	piperidinyl	2-((CH$_3$CH$_2$)NHCH$_2$)phenyl
332.	piperidinyl	2-((CH$_3$CH$_2$)$_2$NCH$_2$)phenyl
333.	piperidinyl	2-((CH$_3$CH$_2$)N(CH$_3$)CH$_2$)phenyl
334.	piperidinyl	2-(((CH$_3$)$_2$CH)NHCH$_2$)phenyl
335.	piperidinyl	2-(((CH$_3$)$_2$CH)$_2$NCH$_2$)phenyl
336.	piperidinyl	2-((cyclopropyl)NHCH$_2$)phenyl
337.	piperidinyl	2-((cyclopropyl)$_2$NCH$_2$)phenyl
338.	piperidinyl	2-((cyclobutyl)NHCH$_2$)phenyl
339.	piperidinyl	2-((cyclobutyl)$_2$NCH$_2$)phenyl

340. piperidinyl 2-((cyclopentyl)$NHCH_2$)phenyl
341. piperidinyl 2-((cyclopentyl)$_2NCH_2$)phenyl
342. piperidinyl 2-((cyclohexyl)$NHCH_2$)phenyl
343. piperidinyl 2-((cyclohexyl)$_2NCH_2$)phenyl
344. piperidinyl 1-CH_3-2-imidazolyl
345. piperidinyl 2-CH_3-1-imidazolyl
346. piperidinyl 2-((CH_3)$_2NCH_2$)-1-imidazolyl
347. piperidinyl 2-((CH_3)$NHCH_2$)-1-imidazolyl
348. piperidinyl 2-((CH_3CH_2)$NHCH_2$)-1-imidazolyl
349. piperidinyl 2-((CH_3CH_2)$_2NCH_2$)-1-imidazolyl
350. piperidinyl 2-((CH_3CH_2)N(CH_3)CH_2)-1-imidazolyl
351. piperidinyl 2-(((CH_3)$_2CH$)$NHCH_2$)-1-imidazolyl
352. piperidinyl 2-(((CH_3)$_2CH$)$_2NCH_2$)-1-imidazolyl
353. piperidinyl 2-((cyclopropyl)$NHCH_2$)-1-imidazolyl
354. piperidinyl 2-((cyclopropyl)$_2NCH_2$)-1-imidazolyl
355. piperidinyl 2-((cyclobutyl)$NHCH_2$)-1-imidazolyl
356. piperidinyl 2-((cyclobutyl)$_2NCH_2$)-1-imidazolyl
357. piperidinyl 2-((cyclopentyl)$NHCH_2$)-1-imidazolyl
358. piperidinyl 2-((cyclopentyl)$_2NCH_2$)-1-imidazolyl
359. piperidinyl 2-((cyclohexyl)$NHCH_2$)-1-imidazolyl
360. piperidinyl 2-((cyclohexyl)$_2NCH_2$)-1-imidazolyl
361. piperidinyl isopropyl

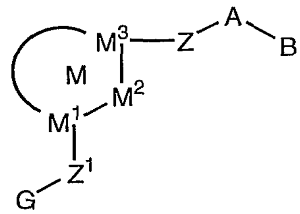
Numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise that as specifically described herein.

WHAT IS CLAIMED IS:

1. A compound of Formula Ia or Ib:



Ia



Ib

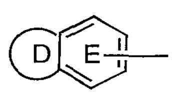
or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

ring M, including M^1, M^2, and, if present, M^3, is a 5 membered aromatic heterocycle, consisting of: carbon atoms, and 1-4 heteroatoms selected from O, $S(O)_p$, N, and NH;

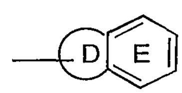
alternatively, ring M is selected from isoxazoline, isothiazoline, pyrazoline, triazoline, and tetrazoline;

ring M is substituted with 0-2 R^{1a};

G is a group of formula IIa or IIb:



IIa



IIb

ring D, including the two atoms of Ring E to which it is attached, is a 5-6 membered non-aromatic ring consisting of carbon atoms, 0-1 double bonds, and 0-2 N, and D is substituted with 0-2 R;

alternatively, ring D, including the two atoms of Ring E to which it is attached, is a 5-6 membered aromatic system consisting of carbon atoms and from 0-2 heteroatoms

selected from the group consisting of N, O, and S, and D is substituted with 0-2 R;

E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, and is substituted with 0-2 R;

R is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl$)_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl$)_2$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3;

alternatively, the bridging portion of ring D is absent, ring E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, and ring E is substituted with R^a and R^b;

R^a is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl$)_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl$)_2$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3;

R^b is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl$)_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl$)_2$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3;

alternatively, R^a and R^b combine to form methylenedioxy or ethylenedioxy;

alternatively, the bridging portion of ring D is absent, and ring E is selected from pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, triazolyl, thiophenyl, and thiazolyl, and ring E is substituted with 0-2 R^c;

R^c is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2CH_3$, CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl$)_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), $CH_2CH_2N(C_{1-3}$ alkyl$)_2$, $(CR^8R^9)_tNR^7R^8$, $(CR^8R^9)_tC(O)NR^7R^8$, and OCF_3;

Z is selected from a bond, $-(CR^2R^{2a})_{1-4}-$, $(CR^2R^{2a})_qO(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qNR^3(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qC(O)(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qC(O)O(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qOC(O)(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qC(O)NR^3(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qNR^3C(O)(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qOC(O)O(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qOC(O)NR^3(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qNR^3C(O)O(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qNR^3C(O)NR^3(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qS(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qS(O)(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qS(O)_2(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qSO_2NR^3(CR^2R^{2a})_{q^1}$, $(CR^2R^{2a})_qNR^3SO_2(CR^2R^{2a})_{q^1}$, and $(CR^2R^{2a})_qNR^3SO_2NR^3(CR^2R^{2a})_{q^1}$, wherein $q + q^1$ total 0, 1, or 2, provided that Z does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

Z^1 is selected from $(CR^3R^{3a})_{1-5}$, $(CR^3R^{3a})_{0-2}CR^3=CR^3(CR^3R^{3a})_{0-2}$, $(CR^3R^{3a})_{0-2}C\equiv C(CR^3R^{3a})_{0-2}$, $(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w$,

$(CR^3R^{3a})_uC(O)O(CR^3R^{3a})_w$, $(CR^3R^{3a})_uO(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3C(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uOC(O)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3C(O)O(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3C(O)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3C(S)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3S(O)_2(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2NR^3(CR^3R^{3a})_w$, and $(CR^3R^{3a})_uNR^3S(O)_2NR^3(CR^3R^{3a})_w$, wherein u + w total 0, 1, 2, 3, or 4, provided that G_1 does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

R^{1a} is selected from H, $-(CH_2)_r-R^{1b}$, $-CH=CH-R^{1b}$, NCH_2R^{1c}, OCH_2R^{1c}, SCH_2R^{1c}, $NH(CH_2)_2(CH_2)_tR^{1b}$, $O(CH_2)_2(CH_2)_tR^{1b}$, $S(CH_2)_2(CH_2)_tR^{1b}$, $S(O)_p(CH_2)_rR^{1d}$, $O(CH_2)_rR^{1d}$, $NR^3(CH_2)_rR^{1d}$, $OC(O)NR^3(CH_2)_rR^{1d}$, $NR^3C(O)NR^3(CH_2)_rR^{1d}$, $NR^3C(O)O(CH_2)_rR^{1d}$, and $NR^3C(O)(CH_2)_rR^{1d}$, provided that R^{1a} forms other than an N-halo, N-N, N-S, N-O, or N-CN bond;

alternatively, when two R^{1a}'s are attached to adjacent atoms, together with the atoms to which they are attached they form a 5-7 membered ring consisting of: carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, this ring being substituted with 0-2 R^{4b} and comprising: 0-3 double bonds;

R^{1b} is selected from H, C_{1-3} alkyl, F, Cl, Br, I, -CN, -CHO, $(CF_2)_rCF_3$, $(CH_2)_rOR^2$, NR^2R^{2a}, $C(O)R^{2c}$, $OC(O)R^2$, $(CF_2)_rCO_2R^{2a}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $C(=NR^{2c})NR^2R^{2a}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NHR^{2b}$, $NR^2C(O)_2R^{2a}$, $OC(O)NR^{2a}R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NR^2(CH_2)_rOR^2$, $SO_2NR^2R^{2a}$, $NR^2SO_2R^{2b}$, C_{3-6} carbocycle substituted with 0-2 R^{4a}, and 5-10 membered

heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-2 R^{4a}, provided that R^{1b} forms other than an N-halo, N-N, N-S, N-O, or N-CN bond;

R^{1c} is selected from H, $CH(CH_2OR^2)_2$, $C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $S(O)R^{2b}$, $S(O)_2R^{2b}$, and $SO_2NR^2R^{2a}$;

R^{1d} is selected from C_{3-6} carbocycle substituted with 0-2 R^{4a}, and 5-10 membered heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-2 R^{4a}, provided that R^{1d} forms other than an N-N, N-S, or N-O bond;

R^2, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic group substituted with 0-2 R^{4b}, a C_{3-6} carbocyclic-CH_2- residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic group comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2a}, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic group substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic group comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic group substituted

with 0-2 R^{4b}, and 5-6 membered heterocyclic group comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic group substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic group comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and comprising carbon atoms and from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3b}, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3c}, at each occurrence, is selected from C_{1-4} alkyl, and phenyl;

R^{3d}, at each occurrence, is selected from H, C_{1-4} alkyl, C_{1-4} alkyl-phenyl, and $C(=O)R^{3c}$;

A is selected from:

C_{3-10} carbocyclic group substituted with 0-2 R^4, and

5-12 membered heterocyclic group comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

B is selected from: H, Y, and X-Y, provided that Z and B are attached to different atoms on A;

X is selected from $-(CR^2R^{2a})_{1-4}-$, $-CR^2(CR^2R^{2b})(CH_2)_t-$, $-C(O)-$, $-C(=NR^{1c})-$, $-CR^2(NR^{1c}R^2)-$, $-CR^2(OR^2)-$, $-CR^2(SR^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-SCR^2R^{2a}-$, $-S(O)CR^2R^{2a}-$, $-S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S-$, $-CR^2R^{2a}S(O)-$, $-CR^2R^{2a}S(O)_2-$, $-S(O)_2NR^2-$, $-NR^2S(O)_2-$, $-NR^2S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S(O)_2NR^2-$, $-NR^2S(O)_2NR^2-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)O-$, $-OC(O)NR^2-$, $-NR^2C(O)NR^2-$, $-NR^2-$, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

Y is selected from:

C_{3-10} carbocyclic group substituted with 0-2 R^{4a}, and

5-12 membered heterocyclic group comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, $(CH_2)_rF$, $(CH_2)_rCl$, $(CH_2)_rBr$, $(CH_2)_rI$, C_{1-4} alkyl,

$(CH_2)_rCN$, $(CH_2)_rNO_2$, $(CH_2)_rNR^2R^{2a}$, $C(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $C(=NS(O)_2R^5)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $C(O)NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, $(CF_2)_rCF_3$, $(CH_2)_r$-CF_3, NCH_2R^{1c}, OCH_2R^{1c}, SCH_2R^{1c}, $N(CH_2)_2(CH_2)_tR^{1b}$, $O(CH_2)_2(CH_2)_tR^{1b}$, $S(CH_2)_2(CH_2)_tR^{1b}$, 5-6 membered carbocycle substituted with 0-1 R^5, and a 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5;

R^{4a}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, $(CF_2)_rCF_3$, $(CH_2)_r$-CF_3, $(CH_2)_r$-F, $(CH_2)_r$-Br, $(CH_2)_r$-Cl, C_{1-4} alkyl, $(CH_2)_rCN$, $(CH_2)_rNO_2$, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $(CH_2)_rN$=$CHOR^3$, $C(O)NH(CH_2)_2NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $C(O)NHSO_2$-C_{1-4} alkyl, $S(O)_pR^5$, 5-6 membered carbocycle substituted with 0-1 R^5, and a 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5;

R^{4b}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$, $(CH_2)_r$-F, $(CH_2)_r$-Cl, $(CH_2)_r$-Br, $(CH_2)_r$-I, C_{1-4} alkyl, $(CH_2)_r$-CN, $(CH_2)_r$-NO_2, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $C(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $NR^3SO_2CF_3$, NR^3SO_2-phenyl, $S(O)_pCF_3$, $S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, $(CH_2)_rCF_3$, and $(CF_2)_rCF_3$;

R^5, at each occurrence, is selected from H, C_{1-6} alkyl, =O, $(CH_2)_rOR^3$, F, Cl, Br, I, -CN, NO_2, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $CH(=NOR^{3d})$, $C(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $NR^3SO_2CF_3$, NR^3SO_2-phenyl, $S(O)_pCF_3$, $S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, $(CF_2)_rCF_3$, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

R^6, at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $C(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;

R^7, at each occurrence, is selected from H, OH, C_{1-4} alkoxycarbonyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

R^8, at each occurrence, is selected from H, C_{1-6} alkyl, and $(CH_2)_n$-phenyl;

alternatively, R^7 and R^8, when attached to the same nitrogen, combine to form a 5-6 membered heterocyclic ring consisting of carbon atoms and 0-2 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^9, at each occurrence, is selected from H, C_{1-6} alkyl, and $(CH_2)_n$-phenyl;

n, at each occurrence, is selected from 0, 1, 2, and 3;

m, at each occurrence, is selected from 0, 1, and 2;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3;

s, at each occurrence, is selected from 0, 1, and 2;

t, at each occurrence, is selected from 0, 1, 2, and 3; and,

alternatively, Z^1 is absent when:

(a) ring M is pyrrole and G is other than phenyl, pyridyl, pyrimidyl, pyrazinyl, or pyridazinyl, substituted with a group selected from CN, $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, $(CR^8R^9)_tC(O)NR^7R^8$, $(CR^8R^9)_tNR^7R^8$, NH_2, $NH(C_{1-3}$ alkyl), $N(C_{1-3}$ alkyl$)_2$, $C(=NH)NH_2$, CH_2NH_2, $CH_2NH(C_{1-3}$ alkyl), $CH_2N(C_{1-3}$ alkyl$)_2$, $CH_2CH_2NH_2$, $CH_2CH_2NH(C_{1-3}$ alkyl), and $CH_2CH_2N(C_{1-3}$ alkyl$)_2$,;

(b) B is H and at least one R^4 is present and is other than amidino, guanidino, amino-ethylene, or amino-propylene group, any of which may be substituted or cyclized; or

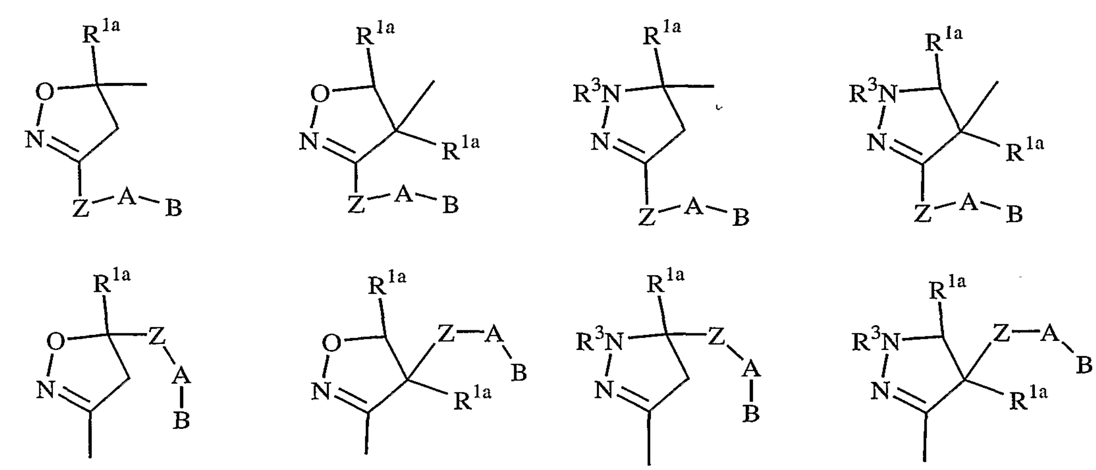
(c) the bridging portion of ring D is absent, and ring E is selected from pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, triazolyl, thiophenyl, and thiazolyl, and ring E is substituted with 0-2 R^c;

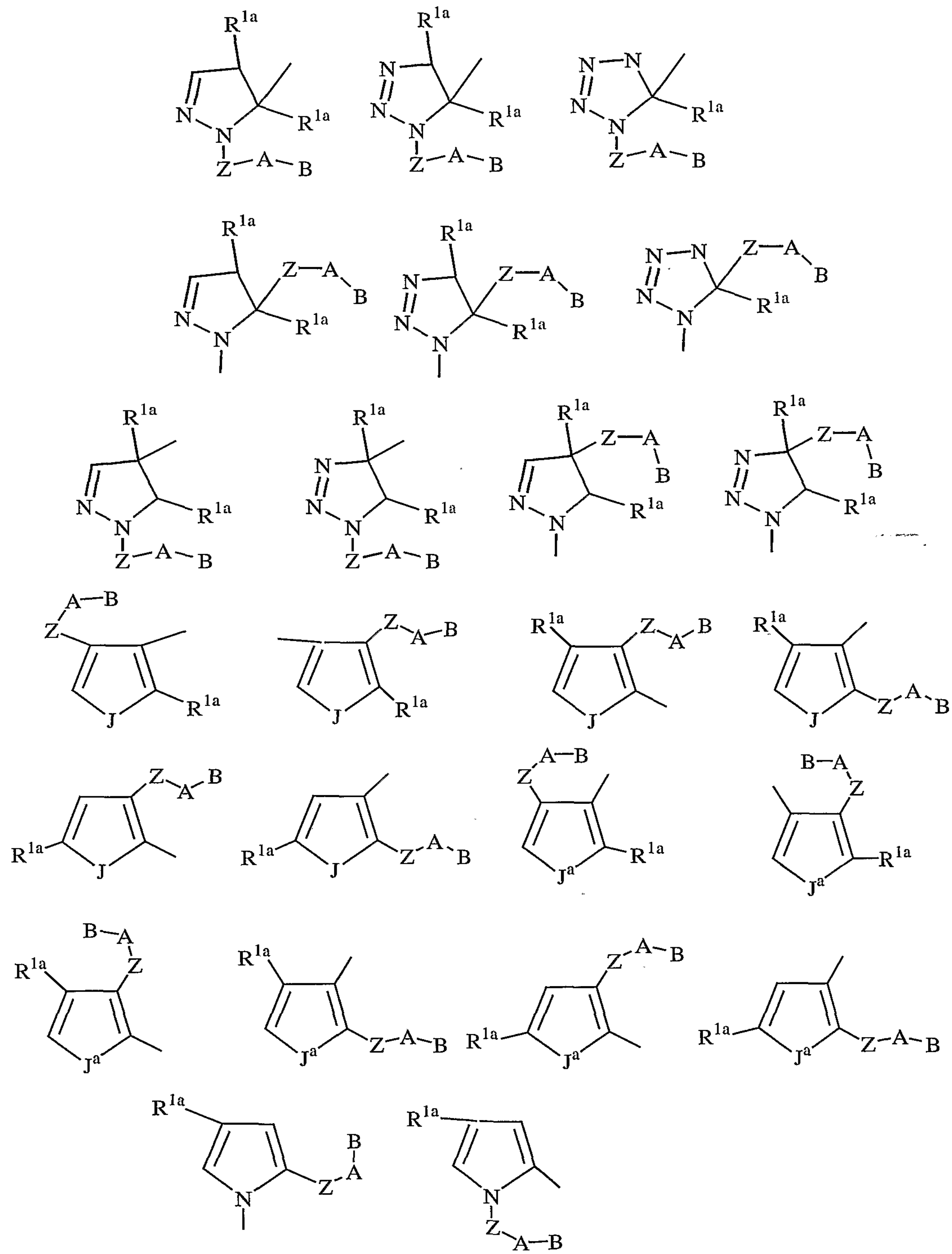
provided that when Z^1 is one of $NHCH_2$, $NHCH_2CH_2$, OCH_2, OCH_2CH_2, SCH_2, and SCH_2CH_2, then G is other than phenyl, pyridyl, pyrimidyl, pyrazinyl, pyradazinyl, and piperidinyl, and Y is other than the group $(CH_2)_rNR^2R^{2a}$ or an unsubstituted pyrrolidine, unsubstituted pyrazolidine, unsubstituted imidazolidine, unsubstituted oxazolidine, unsubstituted isoxazolidine, unsubstituted thiazolidine, and unsubstituted isothiazolidine;

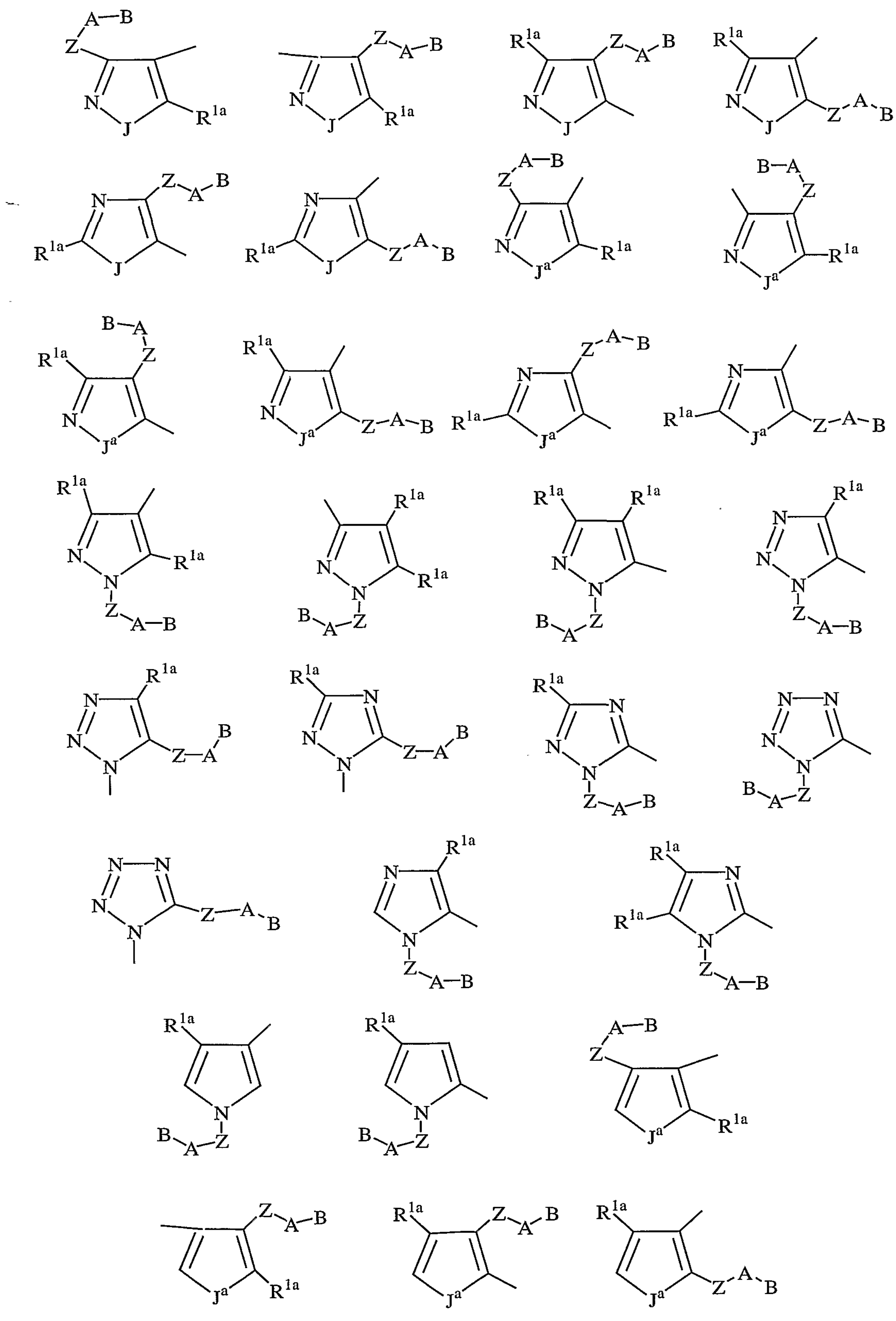
provided that when D is absent and B comprises a phenoxy, thiophenyl, sulfinylphenyl, sulfonylphenyl, carboxyphenyl, phenyoxymethyl, or a sulfonamido group, then at least one of R^a and R^b comprises an amino group, an amido group, a nitrilo group, an amidino group, or a guanidino group.

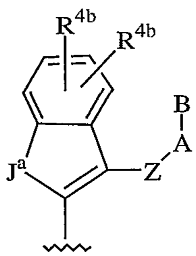
2. A compound according to Claim 1, wherein:

M-Z-A-B is selected from the group:





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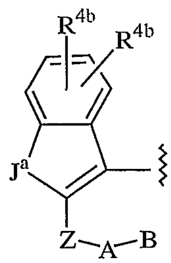
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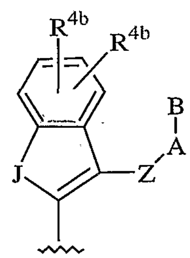
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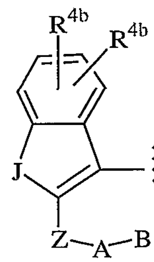
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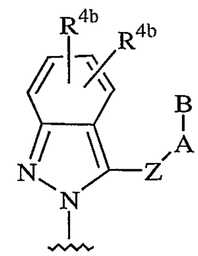
and


aaa

J is O or S;

J^a is NH or NR^{1a};

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^4;

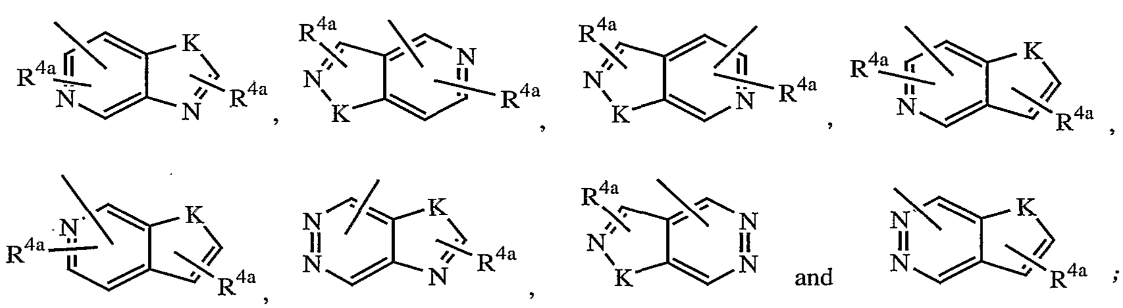
phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

X is selected from $-(CR^2R^{2a})_{1-4}-$, $-C(O)-$, $-C(=NR^{1c})-$, $-CR^2(NR^{1c}R^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)NR^2-$, $-NR^2-$, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

Y is selected from one of the following carbocyclic and heterocyclic systems that are substituted with 0-2 R^{4a};

cyclopropyl, cyclopentyl, cyclohexyl, phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

alternatively, Y is selected from the following bicyclic heteroaryl ring systems:



K is selected from O, S, NH, and N;

Z is selected from a bond, CH_2O, OCH_2, NH, CH_2NH, $NHCH_2$, $CH_2C(O)$, $C(O)CH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that Z does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

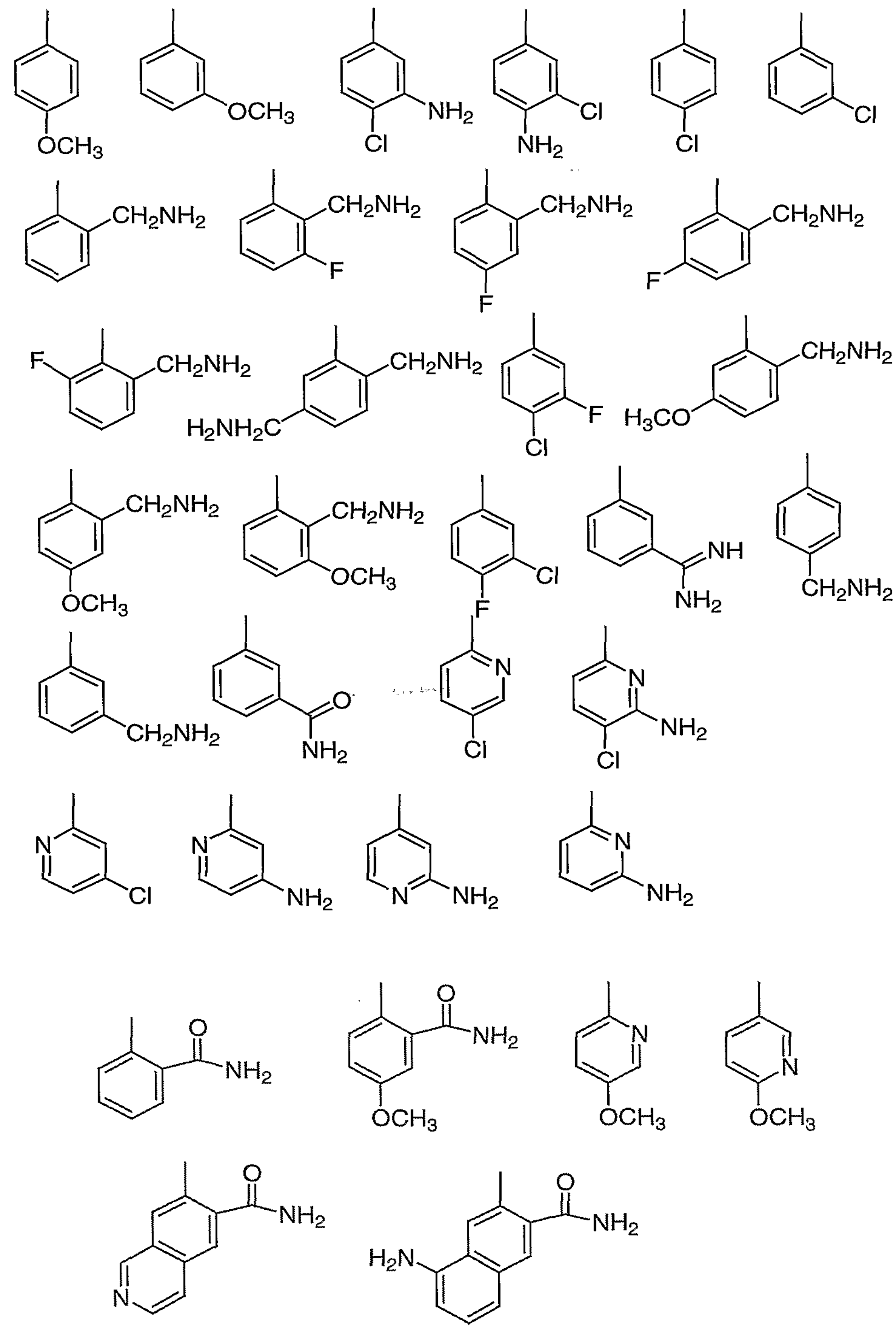
Z^1 is selected from $(CR^3R^{3a})_{1-3}$, $(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uO(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uC(O)NR^3(CR^3R^{3a})_w$, $(CR^3R^{3a})_uNR^3C(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)_2(CR^3R^{3a})_w$, $(CR^3R^{3a})_uS(O)NR^3(CR^3R^{3a})_w$, and $(CR^3R^{3a})_uS(O)_2NR^3(CR^3R^{3a})_w$, wherein u + w total 0, 1, or 2, provided that G_1 does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

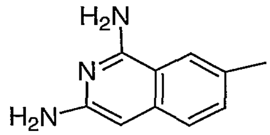
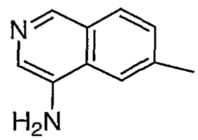
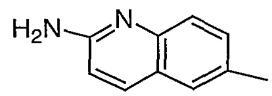
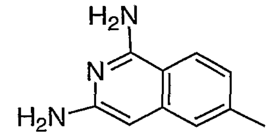
R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $C(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, CF_3, NCH_2R^{1c}, OCH_2R^{1c}, SCH_2R^{1c}, $N(CH_2)_2(CH_2)_tR^{1b}$, $O(CH_2)_2(CH_2)_tR^{1b}$, $S(CH_2)_2(CH_2)_tR^{1b}$, 5-6 membered carbocycle substituted with 0-1 R^5, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5;

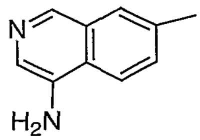
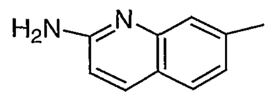
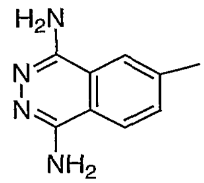
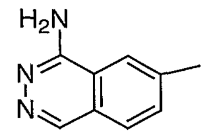
R^{4a}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, CF_3, F, Br, Cl, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $C(O)NHSO_2$-C_{1-4} alkyl, $S(O)_pR^5$, 5-6 membered carbocycle substituted with 0-1 R^5, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5.

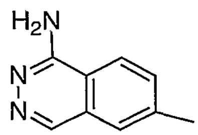
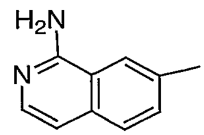
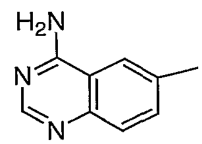
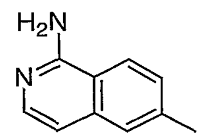
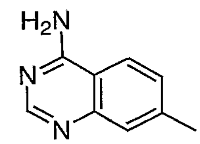
3. A compound according to Claim 2, wherein:

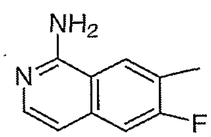
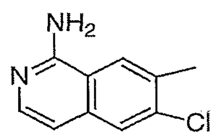
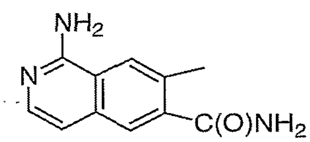
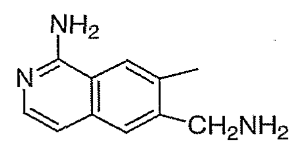
G is selected from the group:

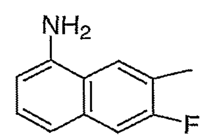
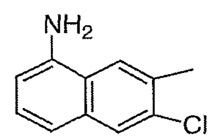
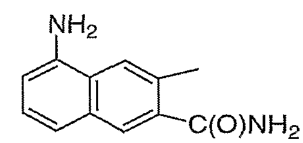
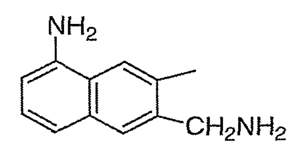


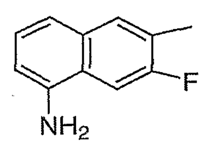
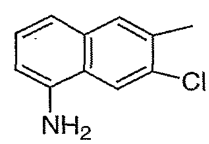
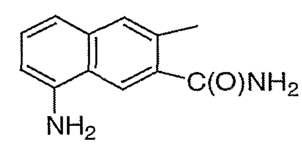
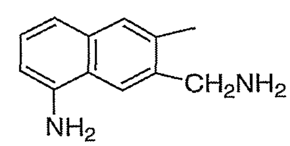
   

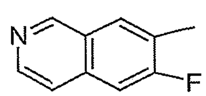
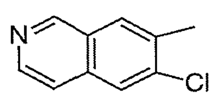
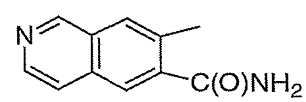
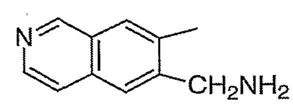
   

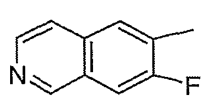
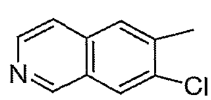
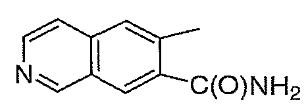
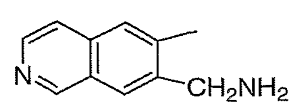
    

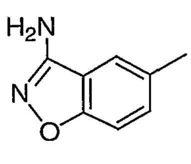
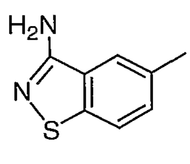
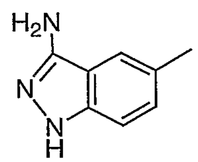
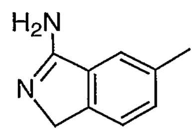
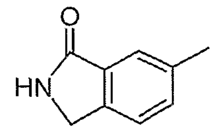
   

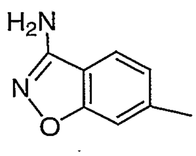
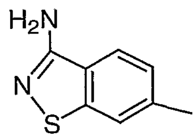
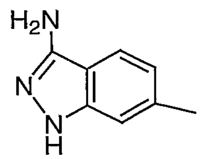
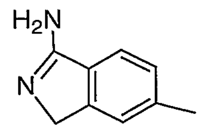
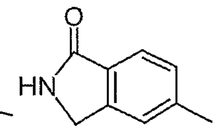
   

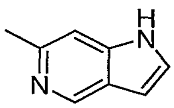
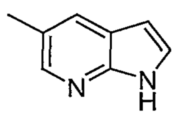
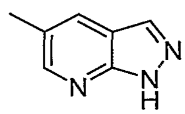
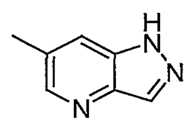
   

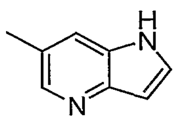
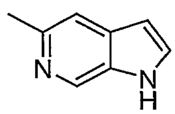
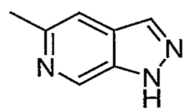
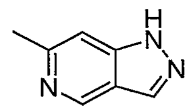
   

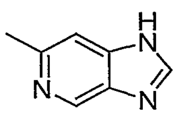
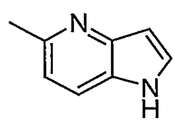
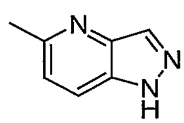
   

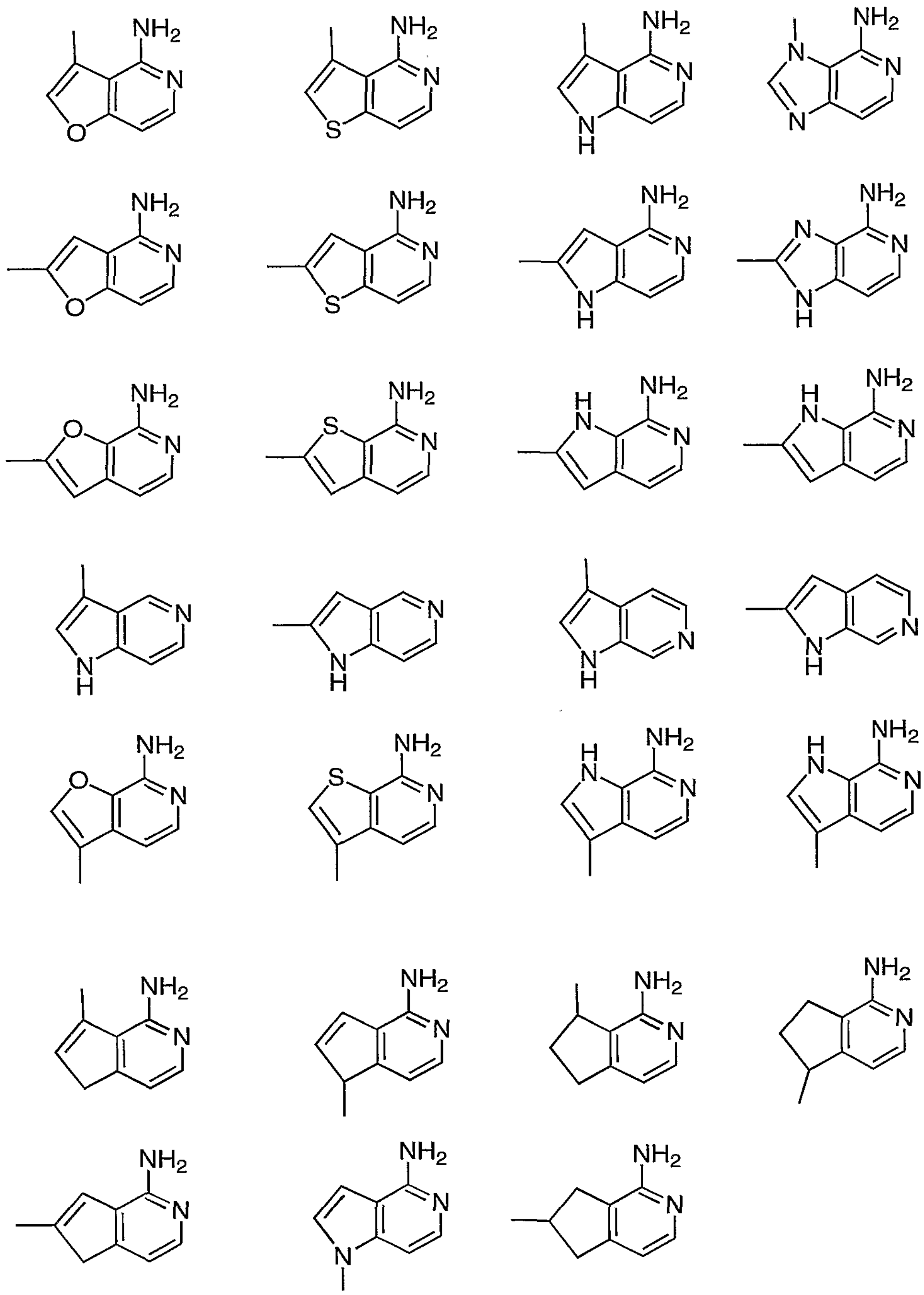
    

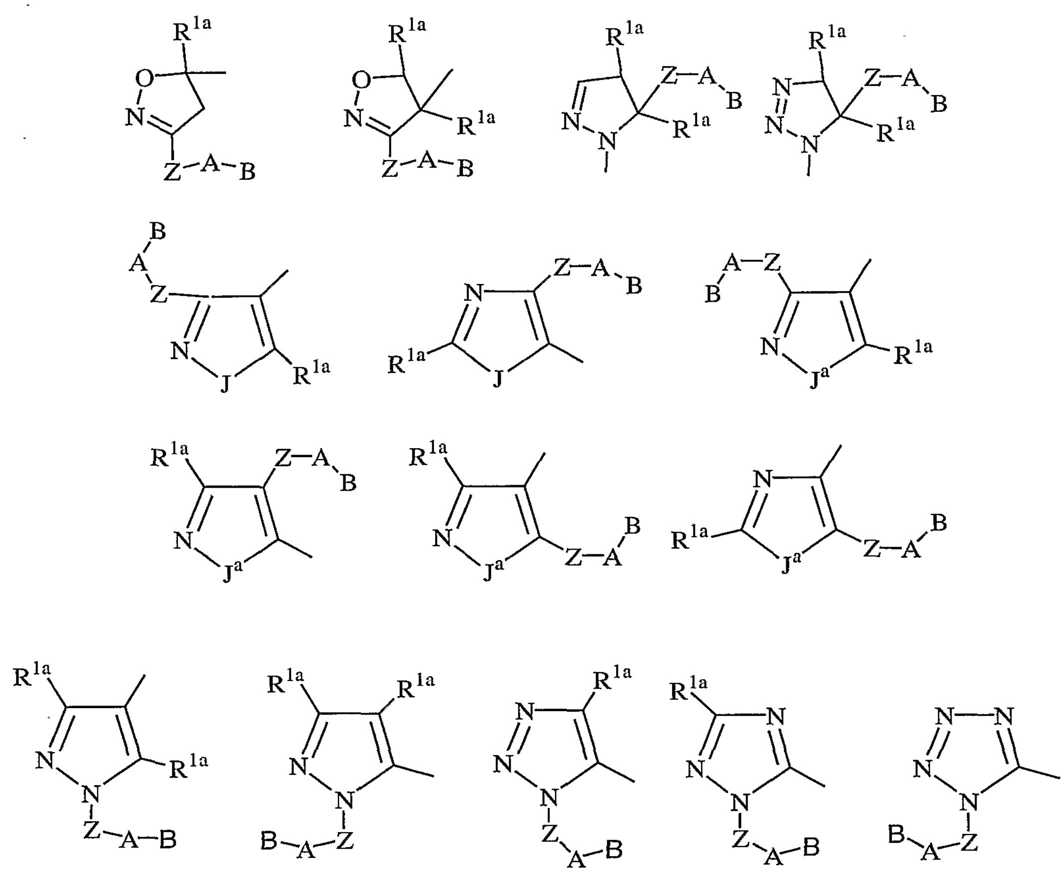
   



M-Z-A-B is selected from the group:



Y is selected from one of the following carbocyclic and heterocyclic rings that are substituted with 0-2 R^{4a};

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, 1,3,4-triazole, benzofuran, benzothiofuran, indole, benzimidazole, benzimidazolone, benzoxazole, benzthiazole, indazole, benzisoxazole, benzisothiazole, and isoindazole;

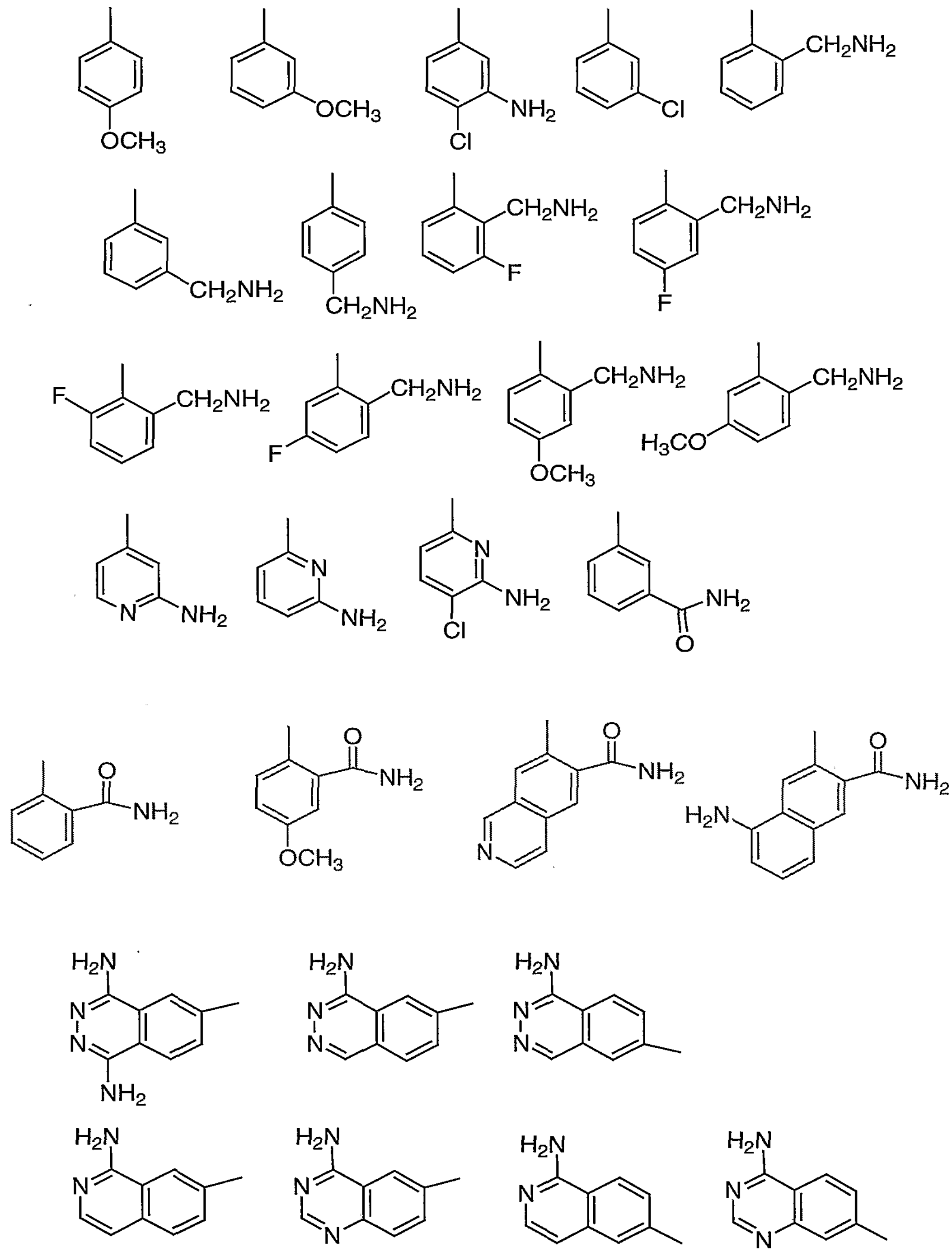
Z is selected from a bond, CH_2O, OCH_2, NH, CH_2NH, $NHCH_2$, $CH_2C(O)$, $C(O)CH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that Z does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

R^4, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $C(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, CF_3, 5-6 membered carbocycle substituted with 0-1 R^5, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5; and,

R^{4a}, at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, CF_3, F, Br, Cl, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $C(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $C(O)NHSO_2$-C_{1-4} alkyl, $S(O)_pR^5$, 5-6 membered carbocycle substituted with 0-1 R^5, and 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5.

4. A compound according to Claim 3, wherein:

G is selected from:


OCH3
OCH3
NH2
Cl
Cl
CH2NH2
CH2NH2
CH2NH2
CH2NH2
F
CH2NH2
F
F
CH2NH2
CH2NH2
F
CH2NH2
OCH3
CH2NH2
H3CO
N
NH2
N
NH2
N
NH2
Cl
NH2
O
O
NH2
O
NH2
OCH3
O
NH2
N
O
NH2
H2N
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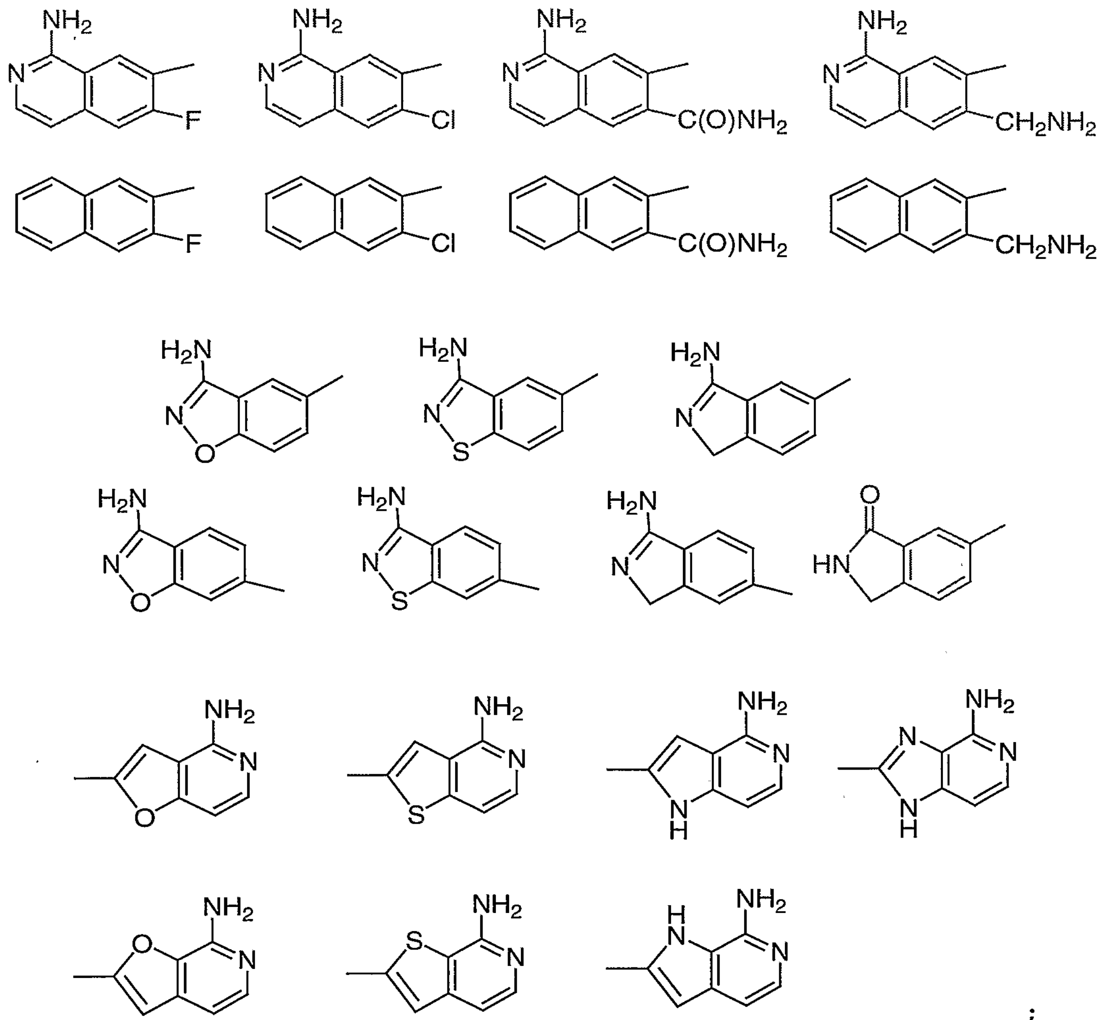
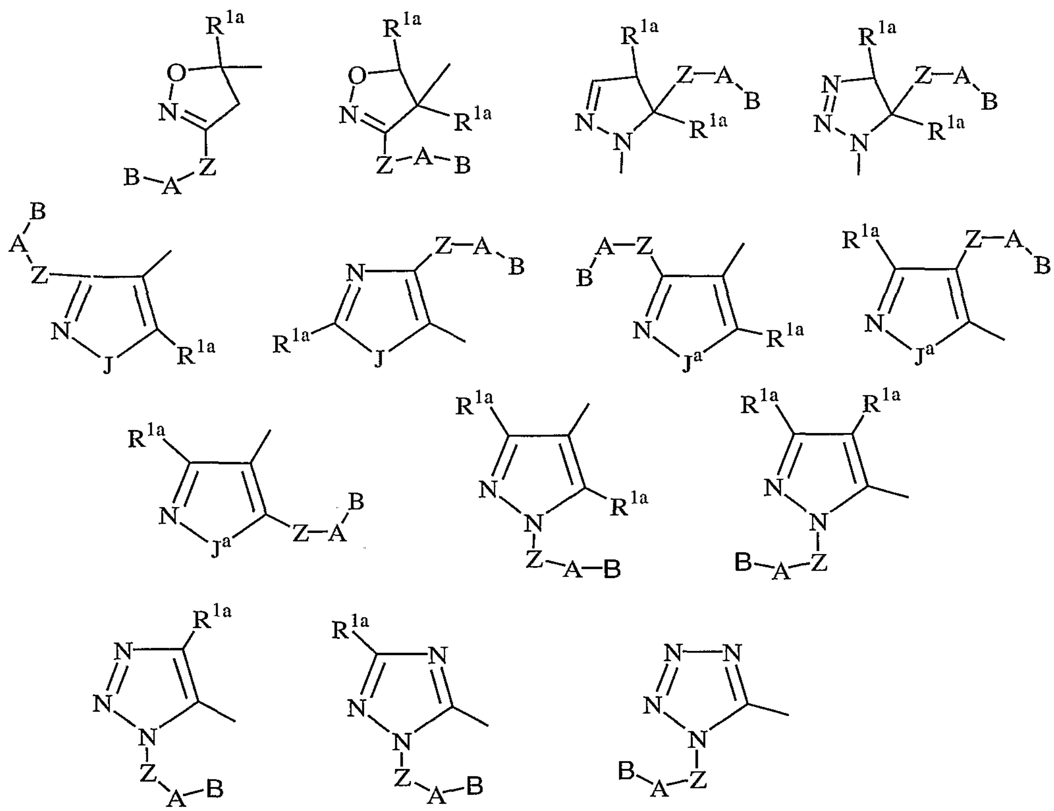


;

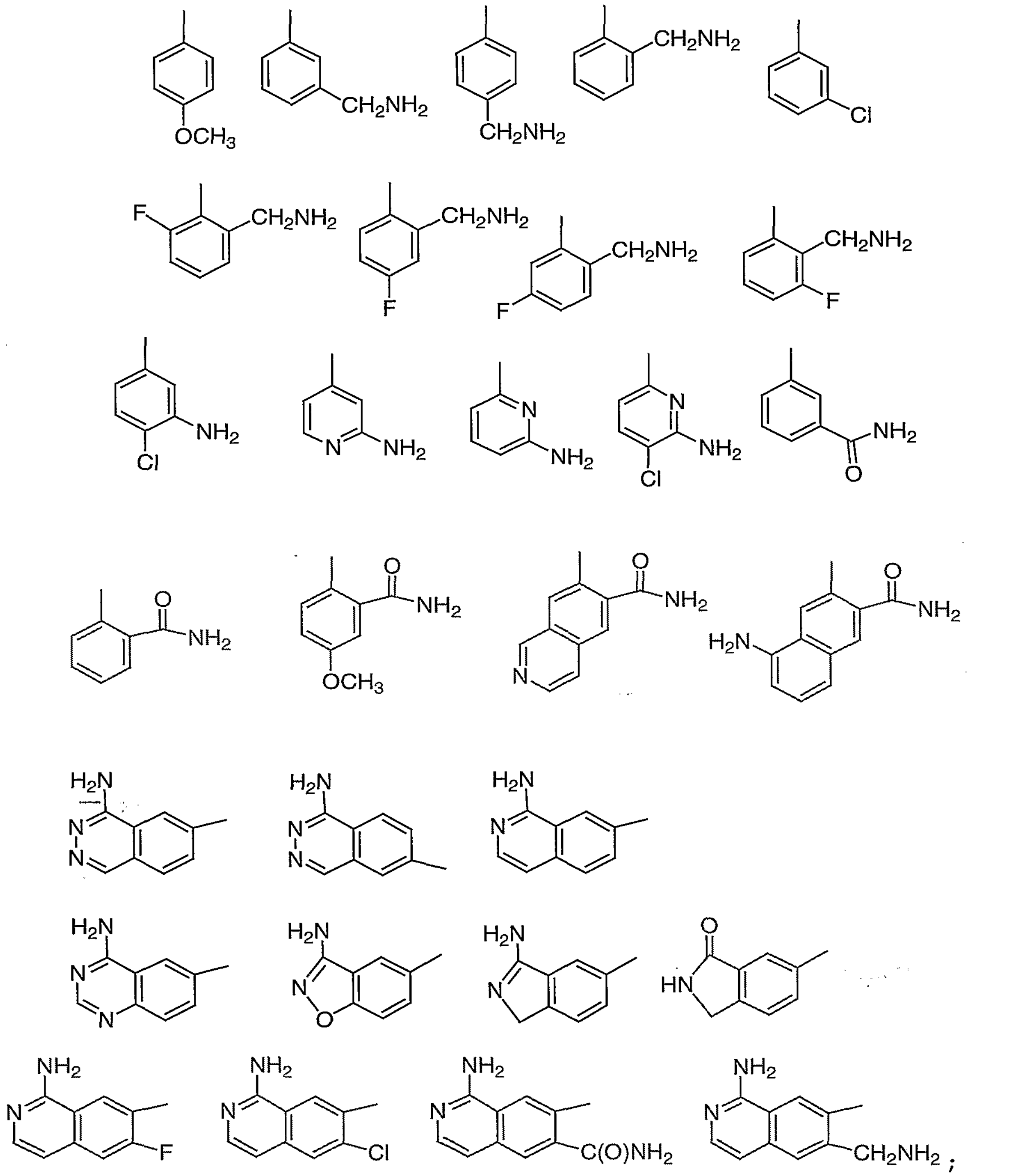
M-Z-A-B is selected from the group:



Z^1 is absent or is selected from CH_2, CH_2CH_2, CH_2O, OCH_2, NH, CH_2NH, $NHCH_2$, $CH_2C(O)$, $C(O)CH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that G_1 does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached.

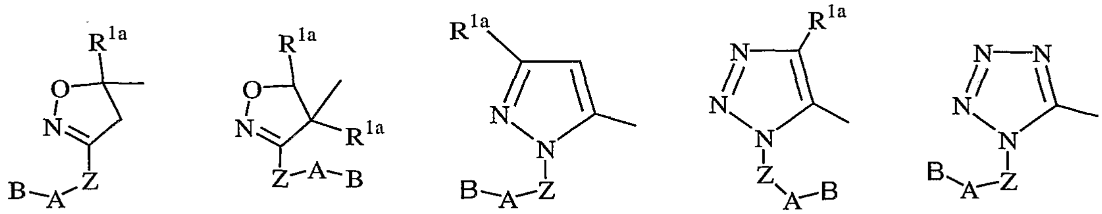
5. A compound according to Claim 4, wherein:

G is selected from:



;

M-Z-A-B is selected from the group:



A is selected from phenyl, pyridyl, piperidinyl, and pyrimidyl, and is substituted with 0-2 R^4; and,

B is selected from phenyl, pyrrolidino, N-pyrrolidino-carbonyl, morpholino, N-morpholino-carbonyl, 1,2,3-triazolyl, imidazolyl, and benzimidazolyl, and is substituted with 0-1 R^{4a};

R^2, at each occurrence, is selected from H, CH_3, CH_2CH_3, cyclopropylmethyl, cyclobutyl, and cyclopentyl;

R^{2a}, at each occurrence, is H or CH_3, and CH_2CH_3;

alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form pyrrolidine substituted with 0-2 R^{4b} or piperidine substituted with 0-2 R^{4b};

R^4, at each occurrence, is selected from OH, OR^2, $(CH_2)OR^2$, $(CH_2)_2OR^2$, F, Br, Cl, I, C_{1-4} alkyl, NR^2R^{2a}, $(CH_2)NR^2R^{2a}$, $(CH_2)_2NR^2R^{2a}$, CF_3, and $(CF_2)CF_3$;

R^{4a} is selected from C_{1-4} alkyl, CF_3, OR^2, $(CH_2)OR^2$, $(CH_2)_2OR^2$, NR^2R^{2a}, $(CH_2)NR^2R^{2a}$, $(CH_2)_2NR^2R^{2a}$, SR^5, $S(O)R^5$, $S(O)_2R^5$, $SO_2NR^2R^{2a}$, and 1-CF_3-tetrazol-2-yl;

R^{4b}, at each occurrence, is selected from H, CH_3, and OH;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl, and benzyl; and,

r, at each occurrence, is selected from 0, 1, and 2.

6. A compound according to Claim 5, wherein:

A is selected from the group: phenyl, piperidinyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

B is selected from the group: 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 2-(N,N-dimethylaminomethyl)phenyl, 2-(N-methylaminomethyl)phenyl, 2-(N-ethyl-N-methylaminomethyl)phenyl, 2-(N-pyrrolidinylmethyl)phenyl, 1-methyl-2-imidazolyl, 2-methyl-1-imidazolyl, 2-(dimethylaminomethyl)-1-imidazolyl, 2-(methylaminomethyl)-1-imidazolyl, 2-(N-(cyclopropylmethyl)aminomethyl)phenyl, 2-(N-(cyclobutyl)aminomethyl)phenyl, 2-(N-(cyclopentyl)aminomethyl)phenyl, 2-(N-(4-hydroxypiperidinyl)methyl)phenyl, and 2-(N-(3-hydroxypyrrolidinyl)methyl)phenyl.

7. A compound according to Claim 1, wherein:

5-[(3-Amidinophenyl)aminocarbonyl]-3-[1,1']-biphenyl-5-carbomethoxymethylisoxazoline;

5-[(3'-Aminobenzisoxazol-5'-yl))aminocarbonyl]-3-(2'-aminosulfonyl-[1,1']-biphenyl)isoxazoline;

5-Methyl-2-(2'-sulfamoyl-biphenyl-4-yl)-2H-pyrazole-3-carboxylic acid-(3-carbamimidoyl-phenyl)-amidine;

5-Methyl-2-(2'-sulfamoyl-biphenyl-4-yl)-2H-pyrazole-3-carboxylic acid (3-aminomethyl-phenyl)amide;

4-[(5-chloro-2-pyridinylamino)carbonyl]-1*H*-pyrazol-5-yl 1-isopropyl-4-piperidinecarboxamide;

1-(3-Amino-benzo[*d*]isoxazol-5-yl)-4-methyl-1*H*-pyrrole-2-carboxylic acid [4-(2-dimethylaminomethyl-imidazol-1-yl)-2-fluoro-phenyl]-amide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylthio-thiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylsulfoxide-thiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylsulfonyl-thiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-n-butylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-phenylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-isopropylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-propylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-ethylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-cyclopentylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-cyclobutylthiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-(3,4-difluorophenyl)thiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(3-Chlorophenylamino)carbonyl]-2-methylthio thiazole-5-yl 1-isopropyl-4-piperidinecarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylthio-thiazole-5-yl 4-(2'-N,N-dimethylaminomethyl phenyl)phenylcarboxamide;

4-[(5-Chloro-2-pyridinylamino)carbonyl]-2-methylthio-thiazole-5-yl 4-[2'-(4-hydroxypiperidylmethyl) phenyl]phenylcarboxamide;

3-[5-(2′-Methanesulfonylbiphenyl-4-carbonyl)-3-methylpyrazol-1-ylmethyl]benzamidine;

6-Methoxynaphthalene-2-carboxylic acid [1-(3-carbamimidoylbenzyl)-5-methyl-1*H*-pyrazol-3-ylmethyl]amide;

3-{5-Methyl-3-[(naphthalene-2-sulfonylamino)methyl]pyrazol-1-ylmethyl}benzamidine;

3-{3-[(6-Methoxynaphthalene-2-sulfonylamino)methyl-5-methylpyrazol-1-ylmethyl}benzamidine;

3-{3-[(7-Chloronaphthalene-2-sulfonylamino)methyl]pyrazol-1-ylmethyl}benzamidine;

3-{3-[(7-Methoxynaphthalene-2-sulfonylamino)methyl]pyrazol-1-ylmethyl}benzamidine;

1-Isopropylpiperidine-4-carboxylic acid [4-(4-chlorobenzoylamino)furazan-3-yl]amide;

1-Isopropylpiperidine-4-carboxylic acid [5-(4-chlorobenzoylamino)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]amide;

1-Isopropylpiperidine-4-carboxylic acid [4-(5-chloropyridin-2-ylcarbamoyl)-2-methyl-2*H*-pyrazol-3-yl]amide;

1-Isopropylpiperidine-4-carboxylic acid [4-(5-chloropyridin-2-ylcarbamoyl)-2-phenyl-2*H*-pyrazol-3-yl]amide; and,

1-Isopropylpiperidine-4-carboxylic acid [4-(5-chloropyridin-2-ylcarbamoyl)-3-methylisothiazol-5-yl]amide;

or a pharmaceutically acceptable salt form thereof.

8. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, or 7 or a pharmaceutically acceptable salt form thereof.

9. A method for treating or preventing a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, or 7 or a pharmaceutically acceptable salt form thereof.

10. A compound of Claim 1, 2, 3, 4, 5, 6, or 7 for use in therapy.

11. Use of a compound of Claim 1, 2, 3, 4, 5, 6, or 7 for the manufacture of a medicament for the treatment of a thromboembolic disorder.